PAEDIATRIC MEDULLOBLASTOMA- COMPARING CLINICAL PROFILE AND OUTCOME WITH MOLECULAR SUBGROUPS

A thesis dissertation submitted in partial fulfilment of the Dr. MGR Medical University requirements towards MD Paediatric Examinations to be held in April 2015

CERTIFICATE

This is to certify that the dissertation entitled 'Paediatric Medulloblastoma- Comparing Clinical Profile And Outcome With Molecular Subgroups' is a bonafide work done by Dr Leenu Lizbeth Joseph during her academic term – June 2013- May 2015 at the Christian Medical College, Vellore in partial fulfilment of the rules and regulations of the degree of MD Paediatrics Examination of The Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2015.

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ABSTRACT

Background:

Medulloblastoma is the second most common paediatric central nervous system tumour. The treatment is also associated with significant morbidity on a long term basis. We looked at the clinical profile and outcome of children treated for paediatric medulloblastoma under the paediatric haemato-oncology unit and also looked at their molecular subgroups, to see if molecular subgrouping can be used as a better prognostic marker. Quality of life of survivors was analysed using Peds QL.

Methods:

109 paediatric medulloblastoma patients were operated on in the neurosurgery department of this hospital between the years 2004-2014. Of these, 73 patients presented to haemato-oncology for chemotherapy. In addition to this, 3 more patients with biopsy proven medulloblastoma, operated elsewhere, came here for further management. We looked at their clinical profile and outcome in detail. Tumour immunohistochemical markers and histology were used to classify the tumours into WNT, SHH and non WNT/non SHH subgroups. The clinical profile and outcome were compared with the different molecular subgroups. In addition, quality of life of survivors was also analysed using PedsQL, a validated tool for studying quality of life of brain tumour survivors.

Results:

Of the 76 children, 50 completed treatment. Tumour markers were studied in 43 of the 76 tumours, to classify the tumours into molecular subgroups. 26 out of the 43 tumours in our study belonged to the WNT subgroup. Statistical analysis showed that WNT tumours did better than non WNT tumours in terms of survival. However, there was no difference in their quality of life, probably because of standard treatment received by all patients.

Conclusion:

On comparison of clinical profile and outcome with molecular subgroups, WNT subgroup has been shown to have a better outcome compared to the other groups. However quality of life analysis does not show any added advantage. Stepping down of therapy for the tumours with better prognosis might be useful in decreasing the long-term morbidity of survivors.

Keywords: Medulloblastoma, molecular subgroups, immunohistochemical markers, disease remission, recurrence, death, long term sequelae, quality of life.

INTRODUCTION

Medulloblastoma is a small blue round cell tumour which arises, most often, from the posterior cranial fossa. It is the second-most common primary malignant central nervous system tumour world-over in children, forming 35% of all CNS tumours in children, as reported by Packer et al.(1) The incidence varies from population to population; a multicentre study done by Sarkar et al in 2010 has shown that among the paediatric population in India, medulloblastoma accounts for 22.4 % of all CNS tumour, second only to astrocytoma.(2)

The disease has a bimodal distribution, with the maximum numbers presenting between the age groups of 3-4 years, followed by 8-9 years(1). There is a male predominance for medulloblastoma. The most common site for medulloblastoma is the posterior cranial fossa, especially near the 4^{th} ventricle. This classic location of medulloblastoma results in obstruction to the CSF flow leading to hydrocephalus. Children present with features of raised intracranial tension and truncal ataxia, due to obstruction to cerebrospinal fluid flow and the relation to cerebellum respectively(3). Medulloblastoma responds very well to radiotherapy and chemotherapy, second only to germ cell tumours of the CNS in this response to therapy.(4)

Further studies in this field have shown that medulloblastoma with certain characteristics do better than the rest. This has led to various classifications, as well as risk stratification methods based on the same.

Various classification methods have been used for medulloblastoma over the years. The initial classification for medulloblastoma was based on the location of the tumour, i.e, whether vermian or cerebellar. The WHO 2007 classification is based on histology, whereas the Boston consensus conference held in 2010 classified medulloblastoma into 4 subgroups namely sonic hedgehog (SHH), wingless (WNT), group 3 and group 4 based on immunohistochemical markers. (5)(6) This classification is however not yet widely used In India. The four variants have distinct demographics, clinical presentation, genetic abnormalities and outcome, hence the use of the molecular subgrouping helps in better prognostication.

In this study, we looked at the clinical profile of all children with medulloblastoma who were treated under the paediatric haematology-oncology unit of a tertiary care hospital in South India between the years 2004-2014. The clinical presentation, course of illness, treatment details, outcome and late complications of the children were studied in detail. The quality of life of survivors was assessed in addition to this. Molecular subgrouping of these tumours was done with the help of immunohistochemical markers as well as histology, and correlation between the clinical disease course and markers was analysed. We hope that this will help us in better risk stratification of the disease in the future.

AIMS AND OBJECTIVES

1. To study the clinical profile and outcome of children with medulloblastoma who presented to the paediatric haematology-oncology unit for treatment between the years 2004-2014.

2. To look at complications of treatment: both during therapy and late effects.

3. To determine whether the histological and molecular sub typing correlates with clinical presentation and outcome.

4. To assess the quality of life of survivors

REVIEW OF LITERATURE

Introduction:

Childhood malignancies form an important cause of mortality in childhood as the deaths from infectious causes have decreased as a result of better hygiene, health care access and facilities. According to population based studies done by the International Agency for Research on Cancer, malignancies are the 9th most common cause for deaths in the age group 5-14 years. The incidence of childhood malignancies in India ranges from 38-124 per 1,000,000 population according to the 2006 National Cancer Registry Program reports.(2)According to the NCRP reports, the age adjusted rates of incidence for childhood cancer incidence among boys is 18.6-159.6 per million for boys, and 11.3-112.4 per million for girls, between the years 2009-2011. Of these, CNS tumours account for 6.6-19.8 per million among boys and 3.0-16.0 per million among girls for the same time period.(7)Central nervous system tumours form the second most common malignancies in children after haematological malignancies world-over. Incidence of CNS tumours in India varies from 22-25 per million population according to Arora et al. (8)Medulloblastoma is an important tumour among these.

Medulloblastoma was first described by Bailey and Cushing in their article in the 1925 edition of Archives of Neurology and Psychiatry, where they labelled it a “common type of mid-cerebellar glioma of childhood”. Almost a century later, medulloblastoma is still an area of intense clinical research and new advances as it still forms a big chunk of paediatric CNS tumours.(4)

Medulloblastoma has a predilection for posterior cranial fossa involvement, causing obstructive hydrocephalus due to ventricular obstruction, and ataxia as a result of cerebellar involvement. The most common presenting complaints are therefore related to the same: the obstructive hydrocephalus causes raised intracranial tension, resulting in headache, vomiting and cranial nerve palsies, and the cerebellar involvement caused unsteadiness and giddiness.(4) The symptoms may be more non-specific in the younger age group. The common presentation in infants are usually a rapidly increasing head size, and “sun setting sign”, or upward gaze palsy, as a result of dilatation of the ventricles.(1)Vomiting is also a common sign in young infants. Brasme et al studied the mean duration between onset of symptoms and diagnosis of medulloblastoma, and found that the median time interval taken for diagnosis is still 2-3 months. (9)This was in spite of vast advances made in radiological diagnostic techniques, and was attributed to the inconsistency of symptoms in children, and to lack of focal neurological signs and symptoms till late in the disease course. Gerber et al studied whether a longer duration of symptomatic period was associated with worse prognosis in the disease course of medulloblastoma. They found that there was no adverse association between a longer time taken for diagnosis and the clinical prognosis. This study also noticed that patients with non-metastatic, non-aggressive forms of medulloblastoma had a longer time interval between the time of onset of symptoms and the time of diagnosis. (10)

Classification:

Various classification methods have been used for medulloblastoma over the years. The important ones among these are the following:

(1) **Classification based on the site of origin of the tumour**:

Medulloblastoma were initially classified based on their location, into those arising from the cerebellar vermis, or from the lateral cerebellar hemispheres. The cell of origin has been found to be different for medulloblastoma arising from these two sites. Those arising in the cerebellar hemispheres arise from the external granular cell layers of ventricular subependymal matrix whereas the vermian tumours are thought to arise from the Purkinje neurons.Giangaspero and Radner in their 2000 publication have confirmed the same. (11) Polkinghorn and Tarbell, in their publication on the various classification methods used in medulloblastoma have shown that tumours which arise from the external granular layer in the cerebellar hemispheres are dependent on the SHH pathway for proliferation, when compared with those arising from the midline, and are more likely to be showing mutations consistent with SHH pathway.(12) Studies by Gibson et al have also confirmed the same, with GNPCs of the cerebellum being shown as the site of origin of SHH.(13)

(2)Classification based on histology of the tumour:

The WHO 2007 guidelines for classification of medulloblastoma are based on the histology of the tumour. This classification had the following categories: classical, desmoplastic, medulloblastoma with extensive nodularity, anaplastic variant and large cell variant. (14)

Classic medulloblastoma is a highly cellular tumor composed of diffuse masses of small, undifferentiated oval or round cells. Some medulloblastoma show neuronal, glial and other differentiation. Neuronal differentiation is manifested by neuropil and rosette formation. Reticulin-free nodules are the characteristic feature of the desmoplastic variant of medulloblastoma.

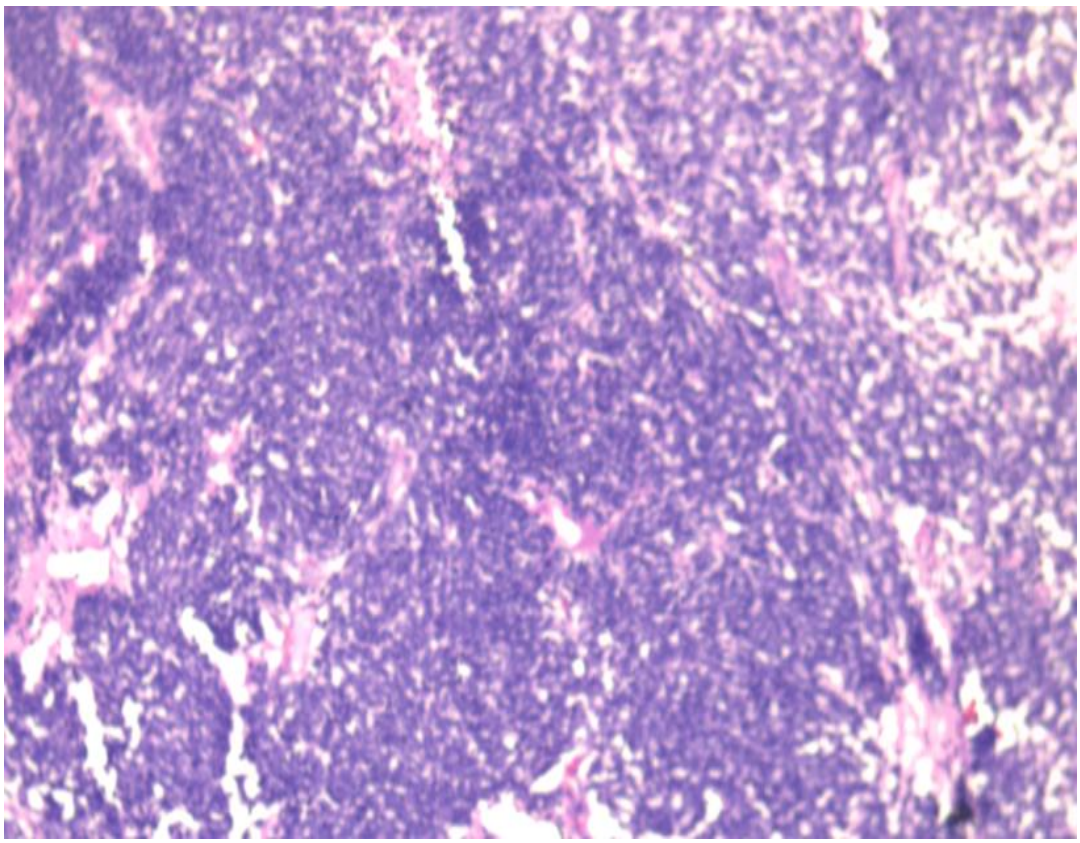


Figure No.1: Photomicrograph of medulloblastoma with classic histology

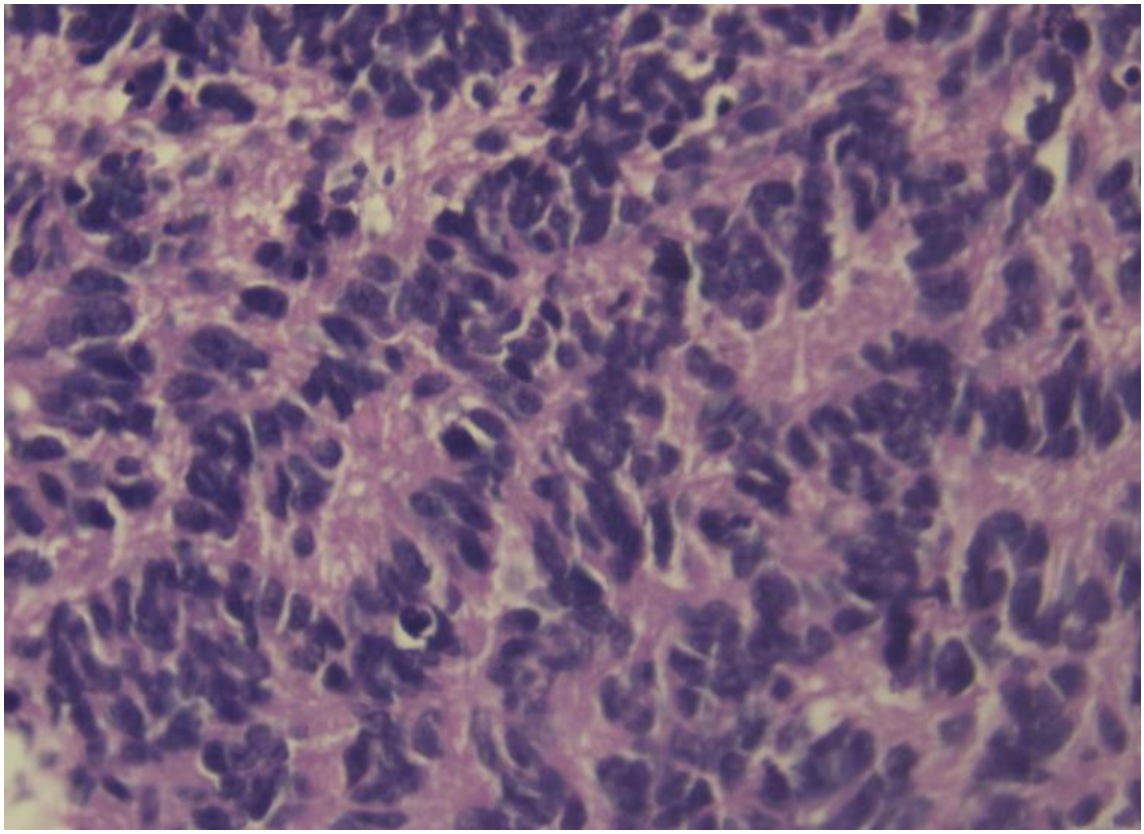


Figure No.2: Photomicrographs demonstrating Homer Wright rosettes in medulloblastoma

Desmoplastic medulloblastoma demonstrates tightly packed cells with neuronal/ astrocytic differentiation. (5) Medulloblastoma with extensive nodularity, on the other hand is characteristically described in the WHO 2007 guidelines as being “different from the desmoplastic nodular variant in exhibition of markedly lobular architecture with markedly decreased inter nodular reticular-free substances.” (15)

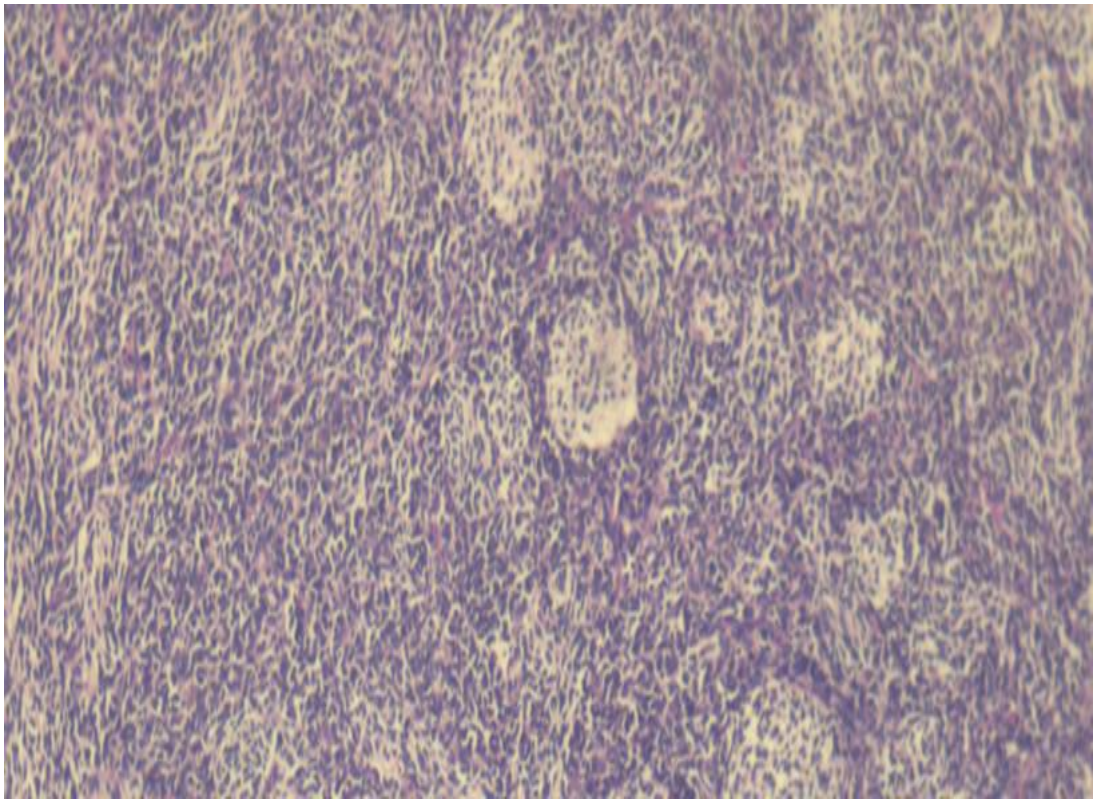


Figure No.3: Photomicrograph of desmoplastic medulloblastoma: showing the nodular pattern

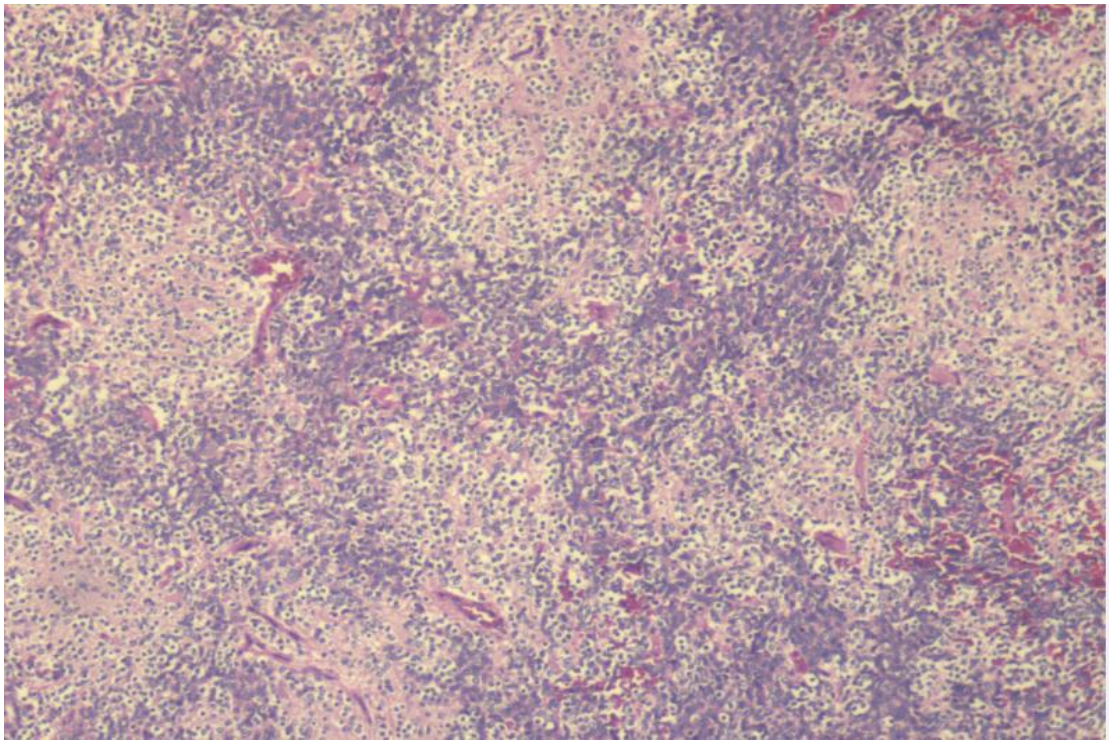


Figure No.4: Photo micrograph of MBEN variant

Cells belonging to the large cell variant of medulloblastoma have nuclei which are large and pleomorphic with prominent nucleoli, with abundant cytoplasm according to Louis et al. (16)

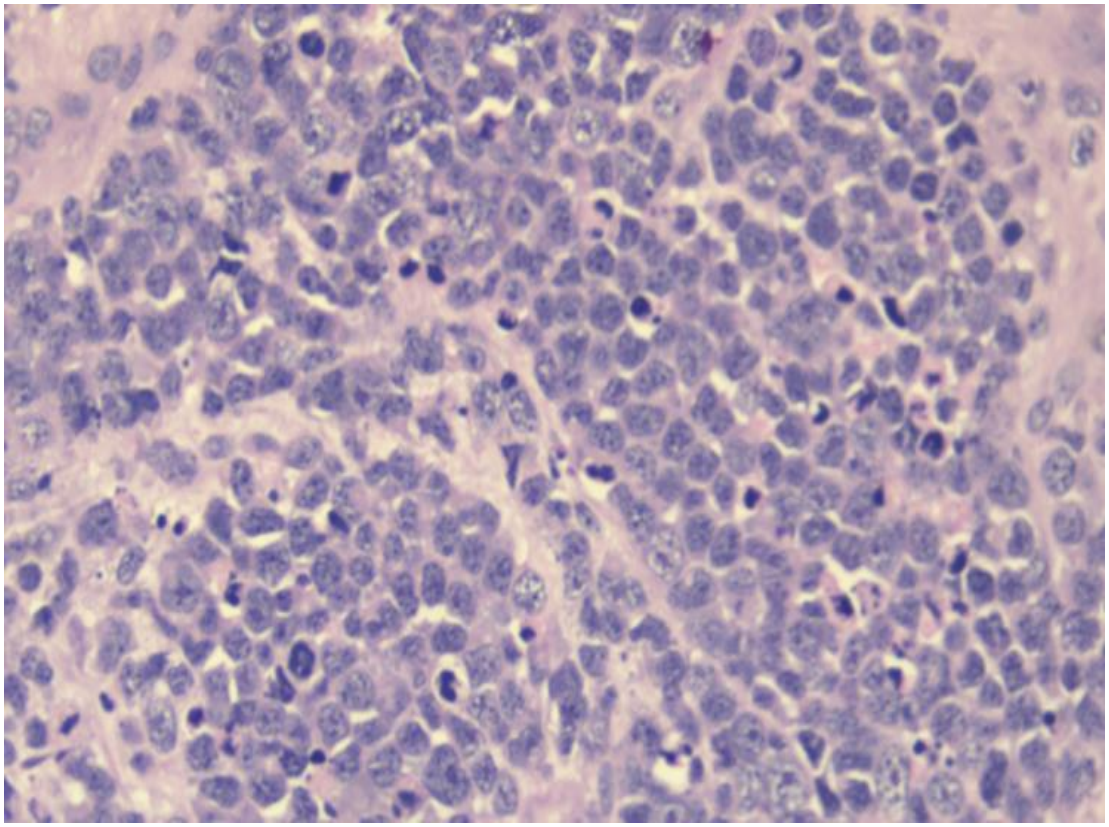


Figure No. 5: Photomicrograph showing large cell variant of medulloblastoma with large, pleomorphic nuclei with prominent nucleoli, and abundant cytoplasm.

Louis et al also elaborates as to how anaplastic medulloblastoma has large tumour cells with prominent nucleoli, abundant mitotic figures and multiple apoptotic bodies. (14)

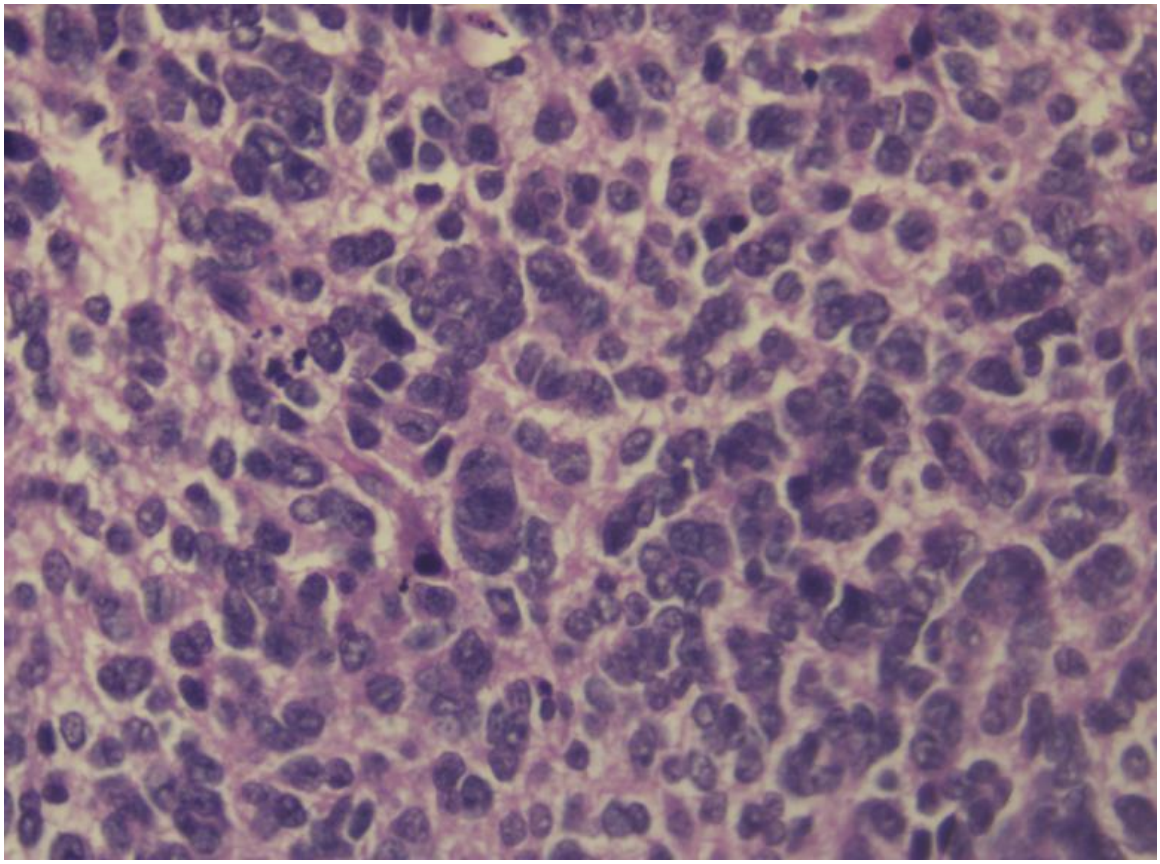


Figure No. 6: Photomicrograph of anaplastic variant of medulloblastoma showing large tumour cells with prominent nucleoli

Massimino et al in their study have shown how those with desmoplastic and classical variants had a better prognosis when compared with those who had anaplastic and large cell variants.(17)This study looked at a total of 125 patients over 10 years, who received standard treatment as per protocol, before more aggressive treatment was commenced for anaplastic variants. For those with medulloblastoma with desmoplastic variant, the overall survival at 5 years was 81 %, and for the MBEN variant, the overall survival was 91.3 %. The overall survival for the anaplastic variants for the same duration, however, was only 44.4 %, which was statistically significant. Further, studies by Verma et al, which are based on data derived from the Childhood Brain Tumour Consortium database have also shown a clear

association between longer disease free survival among those with desmoplastic medulloblastoma, when compared with those with all other subtypes. This study looked at 556 medulloblastoma patients with the comparison groups being desmoplastic medulloblastoma, and medulloblastoma of other subtypes. The histological features associated with good prognosis according to this study(with statistically significant differences, were the presence of high density fine fibrillary stroma, and the presence of nodular and ball like appearance as well as absence of necrosis and prominent nucleoli. (5)

Anaplastic medulloblastoma was shown to have an aggressive course and worse outcome in studies conducted by Eberhart et al. This study looked at 67 medulloblastoma cases from the John Hopkins database, and the pathology tissue specimens which fit the criteria for further histochemical analysis were identified and studied in detail. C- myc expression had statistically significant associated with shorter survival, as was severe anaplasia. Survival rates were increased with lower n-myc and higher TrKc expression, however this difference was not statistically significant.(18)Caputy et al retrospectively studied the clinical, histologic and biologic features of 54 medulloblastoma which were treated in Children's Hospital National Medical Centre and Georgetown University Medical Centre, Washington D.C. found that tumours which showed necrosis, i.e, those with high turnover rates, usually anaplastic variant, had a statistically significant poorer outcome when compared with the rest. This study also showed a higher proportion of recurrence free disease among those who had well differentiated tumours.(19)Leonard et al in their studies of the large cell/anaplastic variant and medullomyoblastoma showed worse prognosis and higher rates of CSF dissemination among them when compared to the other histological variants of medulloblastoma.(20)

(3)Classification based on molecular subgrouping:

Identification of various histological types as prognostic markers was found to be inadequate, as it was found that certain patients did well, inspite of residual tumour post-operatively and even metastases at the time of diagnosis, whereas certain others did badly irrespective of extensive aggressive treatment. This lead to the realisation that there were other, more important and more significant markers of the nature of the disease and the prognosis, other than histology.(21) The search for better classification methods, which were more prognostic in nature was sought as it was found that even though survival rates had increased probably due to better and more aggressive treatment, the survivors suffered significant sequelae in the form of cognition deficits, hearing loss, endocrine insufficiencies etc. The consensus among paediatric oncologists, therefore, was to step down therapy accordingly for tumours with an overall better prognosis to decrease the morbidity of sequelae in survivors, as evaluated by Oyharcabal Bourden et al.(22) However, the histological classification was not sufficient to accurately predict the course of the tumour. Transcriptional studies on medulloblastoma have been happening over the last decade, and it was finally decided during the Boston Consensus conference of 2010 to classify medulloblastoma based on their immunohistochemical properties into 4 subgroups: WNT(wingless), SHH(sonic hedgehog), Group 3 and Group 4. Each of these subtypes have distinct demographics, clinical presentation, associated genetic abnormalities as well as final outcome, as detailed by Taylor et al in their landmark paper in Acta Neuropathologica.(6) With the help of immunohistochemical markers, the tumour can be divided into these 4 subgroups, which will not only help in prognostication, but also in targeted therapies, such as SHH inhibitors for sonic hedgehog group. (23)

Molecular subgroups of medulloblastoma and their characteristics:

(a) WNT subgroup:

Ellison et al have shown that WNT subgroup is seen in older children and young adults. (24) The histology seen in tumours of this subtype is usually classical, and very rarely large cell anaplastic type. There is no gender preponderance. Metastatic disease is rare at the time of presentation. The genetic mutation involved in this subtype is in the CTNNB1 gene mutation, affecting the WNT pathway. MYC gene amplification is seen commonly with this subtype, and the prognosis is good for this subtype. Since the CTNNB1 mutation is responsible for this subgroup, WNT pathway has a strong association with Turcot syndrome, which shares the same mutation, and is associated with familial adenomatosis polyposis of the colon, skin pits and skeletal abnormalities in addition to medulloblastoma.(25)About 15 % of those with Turcot syndrome have WNT pathway medulloblastoma according to Ellison et al who studied this in detail. A strong association between monosomy 6 and WNT pathway has also been noticed by Ellison et al who studied the molecular and clinico-pathological correlation between the various subgroups. (26)

(b) SHH subgroup:

Ellison et al have described how the sonic hedgehog group equally affects males and females, with bimodal incidence among infants and adult.(24)These tumours commonly exhibit desmoplastic histology. Metastases are uncommonly seen at the time of presentation. SMO, SUFU and PTCH1 mutations are commonly seen in this type, affecting the SHH pathway. MYCN gene amplification is the hallmark of this subgroup. Prognosis is good for affected infants, and intermediate for adults. Nevoid basal cell carcinoma syndrome, also called Gorlin syndrome, which is associated with basal cell carcinoma of the

skin, odontogenic keratocysts, other skeletal abnormalities, etc is found in association with this subgroup.

(c) Group 3:

Group 3, commonly involves infants and younger children. Large cell anaplastic and classical type of histology are commonly associated with this subgroup. According to the Boston Consensus Conference, this subgroup usually presents with metastatic disease, and overall prognosis is poor in all age groups. Strong MYC amplification is characteristic of this group.(6)

(d) Group 4:

Group 4, shows a strong male predominance. This type commonly occurs among younger adults as compared to infants and older people. Like Group 3, this group also commonly has large cell anaplastic and classical histology, and is frequently metastatic at the time of diagnosis. Prognosis is intermediate. This group shows minimal MYC or MYCN amplification.(6)

The table given below summarises the common features associated with the molecular subgroups of medulloblastoma:

Table No 1: Characteristics of the 4 molecular subtypes of medulloblastoma

	WNT	SHH	Group 3	Group 4
Age group	Children, young adults	Infants, adults	Infants, Adolescents	Adolescents
Paediatric incidence	10 %	30 %	25 %	35 %
Peak Incidence	Adolescents and young adults	Infants and young adults	First decade of life	Adolescence
Histology	Classic	Desmoplastic/nodular	Classic and large cell anaplastic	Classic
Cell of origin	Lower rhombic lip progenitors	Granule neuron precursors from External Granular Layer, and sub-ventricular zone stem cells	Granule neuron precursors from external granular layer	Unknown
Gender Predilection	Male = Female	Male = Female	Male: Female 2:1	Male: Female 2:1
Radiological characteristics	T2 FLAIR-hyperintense	T2 FLAIR-isointense	Ring enhancing lesions, areas of central	T2 FLAIR-hyperintense

			necrosis	
Syndromic association	Turcot syndrome	Gorlin syndrome	Unknown	Unknown
Associated common mutations	CTNNB1, Wnt pathway mutations, Monosomy 6	PTCH, SUFU, MYCN	MYC amplification	MYCN amplification
Metastases at presentation	Very rare	Unusual	Very frequent	Frequent
Prognosis	Very good	Good	Poor	Intermediate

Overall, there is better prognosis if the tumour belongs to WNT or SHH subtypes rather Group 3 or Group 4, hence it is considered sufficient if the tumours can be categorised Into WNT, SHH or non WNT/non SHH (or Group 3 and Group 4) as shown by Ellison et al. As shown by the same study by Ellison et al, it is sufficient to use any two immuno-histochemical markers to differentiate between WNT, SHH and non WNT- non SHH subgroups of medulloblastoma.

Table No. 2: Immunoreactivity of the various molecular subgroups:

Molecular Group	Immunoreactivity			
	GAB1	β – catenin	Filamin A	YAP1
SHH	Cytoplasmic	Cytoplasmic	Cytoplasmic	Nuclear + Cytoplasmic
WNT	Negative	Nuclear + Cytoplasmic	Cytoplasmic	Nuclear + Cytoplasmic
Non-SHH/WNT	Negative	Cytoplasmic	Negative	Negative

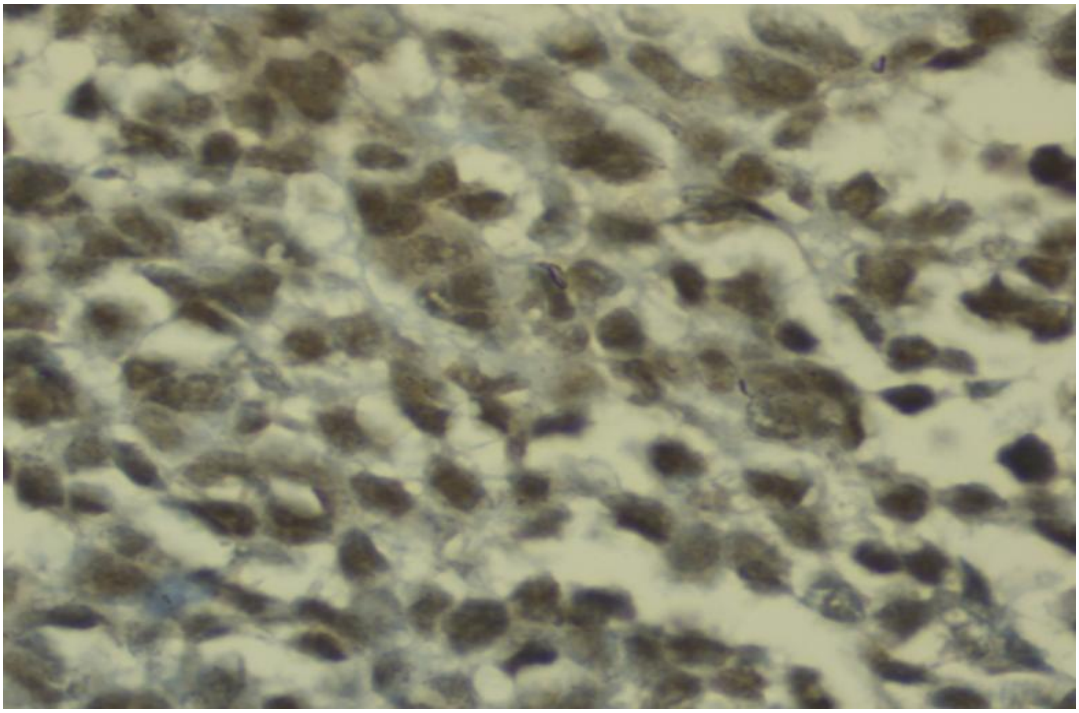


Figure No. 7: Photomicrograph of medulloblastoma with immunopositivity for beta catenin

Even though there are many studies world-over confirming the relationship between the molecular subgroups of medulloblastoma and their varied clinical presentation, course of illness and overall prognosis, there were very few Indian studies confirming the same. In this

study, we have used β-catenin and the histology of the various tumours for molecular subtyping medulloblastoma into WNT, SHH and non WNT-non SHH groups.

Risk stratification:

Risk stratification for any disease is required for prognostication, and it is also the deciding factor in deciding the aggressiveness, duration and the modalities of treatment. The initial classification system was proposed by Chang et al in 1969, which was a modification of the TNM scoring system which was used for other solid organ tumours.(27) The scoring system is as follows:

Chang scoring system for medulloblastoma(28)

(a)Tumour stage

- T1: tumour diameter <3cm, involving one structure in posterior fossa
- T2: tumour diameter <3cm, involving two or more structures posterior fossa structures
- T3a: tumour diameter >3cm, involving two or more structures posterior fossa structures
- T3b: tumour involving floor of the 4th ventricle
- T4: tumour spreading out of the 4th ventricle or presence of severe hydrocephalus

(b) Metastases stage

- M0: no tumour cells in cerebrospinal fluid (CSF)
- M1: presence of tumour cells on CSF cytology
- M2: tumour seeding in intracranial CSF pathways
- M3: tumour seeding in spinal CSF pathways
- M4: systemic spread

According to the Chang system, a higher T stage or M stage prognosticates a worse outcome in terms of survival. This was shown by Zeltzer et al (28)when their study on 203 patients with medulloblastoma showed a significant survival advantage among those with non metastatic disease when compared with those with metastatic disease. Phi et al in their study on CSF metastatic disease in medulloblastoma also showed that metastatic disease played an important role in determining the survival.

The next stratification which came into use was the MAPS scoring system, which as the name indicates, stands for Metastases, Age, Pathology/ histology and Surgery(degree of resection). This stratification method was used in the 1980s, but was less popular than the Chang system of classification. Following this, the next scoring system to come into use was the one elaborated by Sure et al.(29) This method came into vogue in the 1990s, after publication of the results of a study on 66 patients with medulloblastoma who were treated at a single centre using similar surgical methods. The comparison was based on the patient survival as analysed by Kaplan-Meier survival analysis studies. The total score from this system is 20, with the three prognostic groups being those with scores<=6, 7-13 and more than 13. The higher the scores, the better the patient's prognosis according to this study. The parameters used and the scores are provided below(29)

Sure scoring system:

Parameter	Subgroup	Scoring Number
Age	>10 years	2
	0-10 years	0
Location	2a	3
	1a	2

	2b	1
	1b	0
Resection	Total	4
	Subtotal	2
	Partial	1
	Biopsy	0
Metastases	No	3
	Present	0
Histology	Desmoplastic	2
	Classical	0

Where location codes are

1a = Medial with no infiltration

1b = Medial with infiltration

2a = Lateral

2b = Cerebellopontine angle

Based on the scores, three distinct classes were formed, with the one having the highest score having the best prognosis. This study found that their patients who were older than ten years at the time of diagnosis had a better survival rate when compared to those who were less than ten years of age at the time of diagnosis($p < 0.01$). Patients with a more lateral tumour location also did better than those who had a midline tumour, or those with brainstem infiltration ($p<0.05$). Total surgical resection was also associated with a more

favourable outcome when compared with subtotal resection ($p<0.01$) or partial excision (0.001). Patients who had a metastatic disease at the time of presentation also had a worse prognosis than those with non metastatic disease ($p<0.001$). Desmoplastic histology also provided a favourable outcome when compared with classic histology ($p<0.01$).

Current risk stratification:

The current risk stratification for medulloblastoma as proposed by Packer et al is based on the following factors: age at presentation, degree of tumour resection, histology of the tumour and the presence of metastasis (spinal/distal). Of these, age more than 36 months at the time of diagnosis, complete resection of tumour, absence of metastasis and desmoplastic histological variant are associated with good prognosis. (30) Kortmann et al looked at the efficacy of neo-adjuvant chemotherapy before radiotherapy, in comparison with standard RT with concurrent vincristine followed by 8 cycles of chemotherapy regimen.(31) 137 children were randomised into these two groups, and the results were analysed in terms of toxicity of treatment, survival and prognostic factors, both positive and negative. This study found that in irrespective of treatment regimen, those who were between 1.5-3 years did badly, as those with subtotal resection of tumour, thereby confirming the current risk stratification system. Zeltzer et al did a randomised control Phase III study on 203 children with medulloblastoma, on the efficacy of " 8 drugs in one day" before radiotherapy and after radiotherapy, in comparison with Radiotherapy followed by chemotherapy with vincristine, lomustin, cisplatin and prednisolone.(28) Stratification of disease was done using metastatic stage and location of the tumour, as proposed by the Chang system. This study showed the four drug regimen to be superior to the 8 drugs in one day regimen in terms of overall survival as well as event-free survival. In addition, this study

also proved that for children with non metastatic disease, age more than 3 years and residual disease less than 1.5 cm2 are both positive prognostic factors.

Prognostication using biologic markers is being evaluated in many centres. Ellison et al studied the presence of β-catenin as a favourable prognostic marker, and found that nuclear beta catenin positivity is associated with favourable outcome.(32)Similar conclusions were drawn by Fattet et al, however it is still not universally acceptable to step down therapy based on the presence of β-catenin positivity alone.(33)

Shih et al also showed isochromosome 6(loss of one copy of chromosome 6) has a good prognosis in the presence of β-catenin positivity.(34)Gilbertson et al studied the effect of a group of biomarkers on disease prognosis and found high ERbB2 receptor expression and isolated chromosome17 p loss to be associated with bad prognosis. (21)Pan et al, on the other hand, found isochromosome 17q to be a poor prognostic factor in high risk disease.(35)Further, studies by Eberhart et al at John Hopkins Institute found TrkC amplification to have positive prognosis, as against n-myc and c-myc amplifications, which were found in association with tumour anaplasia and worse prognosis.(18)

Shih et al in their studies on prognostic biomarkers, found different prognostic factors for each of the 4 molecular subtypes. (34)Their findings are summarised in the table below:

Table No. 3: Prognostic association of biomarkers with molecular subtypes

	Biomarker	Prognosis
WNT	Isochromosome 6	Good prognosis
SHH	Loss of chromosome 14q GLI2 amplification GLI2 amplification + chromosome 14q- Chromothripsis	Poor prognosis Poor prognosis Poor prognosis Poor prognosis
Group 3	Isochromosome 17q MYC amplification Chromosome 8q loss Chromosome 1q gain	Poor prognosis Poor prognosis Good prognosis Good prognosis
Group 4	10 p loss +loss of chromosome 11 Chromosome 10p loss + gain of chromosome 17 MYCN amplification	Good prognosis Good prognosis No effect

The above table shows how prognostic factors can vary between subgroups as well; hence they should be taken in the context of the subgroup and the histology, and not in isolation.

Treatment of Medulloblastoma

Treatment of medulloblastoma requires a multidisciplinary approach. Lafay-Cousin et al elaborated how the standard of care treatment for medulloblastoma consists of total/ near-total surgical resection followed by radiotherapy and adjuvant high dose multi-agent chemotherapy.(36) However, there is significant short term as well as long term morbidity associated with disease as well the treatment, hence it is essential to stratify the disease prior to commencement of treatment.

Pre-treatment assessment

Pre-treatment assessment includes careful consideration of age of the patient, location of the tumour along with resectability and metastatic stage. MRI is currently considered as the gold standard of imaging of the brain and spine to confirm disease, delineate the extent of the disease and to look for leptomeningeal enhancement. Meyers et al were the first to describe the MR features of medulloblastoma, which included the classic location, high propensity for hydrocephalus, and better demarcation of peri-lesional oedema with the use of contrast enhancement. (37)

MRI features for distinguishing between the molecular subgroups:

Perreault et al have described very precisely the MRI features of the different molecular subgroups, which can be used as surrogates for the immunohistochemical markers pre-operatively(38). This study looked at 47 patients, who were treated at the Stanford University, all of who had pre-operative imaging in the form of MRI as well as tumour histology done post-operatively. 3 separate neuro-radiologists, who were not aware of the histology assessed the MRI images separately. Validation of the MRI features of the

separate subtypes were done by assessing another cohort of 52 paediatric medulloblastoma patients from the hospital for Sick Kids, Toronto.

The MR imaging features that were analysed by Perreault et al were the following: location of the tumour, the pattern of enhancement, presence of any cysts/ cavities, any areas of haemorrhage/ mineralization, any evidence of intracranial or leptomeningeal seeding, the margins of the tumour and any areas of necrosis as evidenced by ring-enhancement. This study showed how WNT tumours were usually seen in the cerebellar peduncle, or in the cerebello-pontine angle. Location of the tumour in cerebellopontine angle was associated with a positive predictive value of 100 % for WNT tumours. SHH tumours on the other hand, were commonly seen along the cerebellar hemisphere. Group 3 and group 4 tumours are more commonly located within the fourth ventricle and usually do not show any enhancement with contrast. Ill defined tumour margins were also documented as a characteristic feature of Group 3 tumours. The presence of cystic areas, necrosis, mineralised areas and areas of haemorrhage were not found to have any statistically significant association with any of the molecular subgroups. Considering the fact that MRI forms the gold standard of diagnosis of medulloblastoma, and is a standard of care diagnostic procedure, this can be used as a pre-op surrogate for molecular subgroups in the future, especially keeping in mind how expensive tumour markers are.(38)

CT myelography as described by Meyer et al, which was being used to detect leptomeningeal involvement in the 1990s is not in vogue anymore. The timing of investigations to detect metastases is also crucial.(37)

Metastatic workup

The two investigations which are commonly used for the detection of leptomeningeal spread are MRI spine and CSF cytology. Harrison et al in their study regarding use of these two modalities, found cytology to be as good as MRI spine, and that there was no superiority in obtaining a sample from the cisterna magna as compared to CSF obtained by a lumbar puncture. (39)Fouladi et al did a comparative study to look at which of these two modalities is more superior at detection of leptomeningeal metastases. The results of this study showed that both were invaluable, and both could miss up to 14 % of metastases if done singly, hence the gold standard is still MRI spine plus CSF cytospin for malignant cells. (40)

The other issue commonly faced while diagnosing metastases was the timing of these investigations. For a long time, it was a common recommendation that these investigations be done after 3-4 weeks of surgery, to avoid spurious results due to blood stained cytospin smears which would be unsatisfactory for evaluation and to avoid missing leptomeningeal thickening and clumping due to blood in the cisterns. However, since radiotherapy starts as early as 2-3 weeks after surgery, the current recommendations by Raleigh et al are that MRI spine for detection of leptomeningeal metastases be done pre-operatively, to prevent post-op artefacts resulting in either over-diagnosis or under-diagnosis as a result of obscuration of the deposits by blood. (25) Cytology is advocated at least 2 weeks after surgery, to prevent false positive results. On the other hand, imaging of the brain to look for post-op residual lesions should be done within 72 hour of surgery so that granulation tissue does not obscure any residual lesions.

Treatment guidelines for medulloblastoma have changed over the years with new advances, however the basic principle remains the same- it is a multidisciplinary approach, utilising neurosurgical expertise for near total excision, followed by adjuvant chemotherapy as per protocol and radiotherapy as per protocol. Pollack et al reviewed this multidisciplinary approach towards medulloblastoma and found that risk adapted treatments for individuals seem to be the current best option for medulloblastoma.(41)

Pre-operative CSF shunt surgery

Due to the fact that medulloblastoma arises most commonly around the fourth ventricle, this tumour has a propensity for hydrocephalus. Albright et al had shown how children who underwent surgical shunting for increased ICP did better in the post-operative period, with significantly decreased mortality than those who did not have a shunt surgery.(42) Schweitzer et al has however raised the possibility of extraneural metastases following a ventriculoperitoneal shunt. (43)However, in a scenario with an imminent risk of tonsillar herniation, or a poor sensorium as a result of raised ICP is present, an emergency CSF drainage is advocated. Muzumdar et al have shown how one-third of those with posterior fossa tumours will need a pre-operative CSF diversion, one third will not need any diversion, and one third will benefit from early surgery alone without any CSF shunt.(23)

The various shunt procedures include ventriculoperitoneal shunts, ventriculoatrial shunts ventriculo-pleural shunts etc. However, what is preferred nowadays, in the presence of a functional CSF absorption pathway is a third ventriculostomy, which can be done intra-operatively as well and has less complications according to Muzumdar et al.(23)When the decision to do a shunt surgery is considered, the possibility of complications such as shunt

infection, blockage, etc should also be considered, and weighed against the benefits and necessity of the shunt surgery. Often anti-oedema measures and early surgery are enough to manage hydrocephalus and its associated complications.

Surgical management

Following appropriate pre-operative workup and stabilization as detailed before, surgical excision is the next in line as treatment of medulloblastoma. Total or near total excision of the tumour is associated with the best outcome according to Lafay-Cousin et al.(36)According to Packer et al, residual disease of <1.5cm2 is considered as standard risk disease. (30)However, extensive resection of the tumour in an attempt to achieve as much local control of the disease may lead to significant neurological deficits post-operatively.

Post-operative complications- posterior fossa syndrome

The most important and common consequence of extensive resection is **posterior fossa syndrome(PFS),** also known as cerebellar mutism. Pitsika et al have explained how the term cerebellar mutism syndrome (CMS) is used to describe a group of symptoms caused by a cerebellar lesion, which includes muteness, ataxia, hypotonia, dysarthria and irritability. Posterior fossa syndrome is a broader term that includes cerebellar mutism as well as movement disorders (ataxia and hypotonia) and a wide spectrum of neurobehavioral abnormalities.(44) Cerebellar mutism may be seen in upto 25 % of children operated for medulloblastoma according to Muzumdar.(23). This is thought to have occurred as a result of interruption of the dentato-thalamo-cortical pathway as a result of extensive surgical resection. Though these children improve usually improve within 2-3 months of surgery, reports of a certain degree of neurological sequelae have been reported by Pitsika et al.(44)

Various risk factors have been postulated for cerebellar mutism by Doxey et al and Grill et al, the important ones being midline location of the tumour, brainstem involvement and a more aggressive and invasive tumour.(45)(46) The others implied commonly are a younger age at diagnosis, a pre-existing language impairment, radical tumour excision, larger tumour size and vermian incision during surgery. The core characteristics of cerebellar mutism are that it is delayed, I.e, the onset is usually after 1-6 days of normal speech post-operatively, and that it is transient, lasting from a few weeks to 6 months. Speech is usually the first symptom to recover, followed by oropharyngeal apraxia (refusal to or inability to swallow inspite of intact gag reflex). The irritability and emotional lability are next to recover.

Wells et al looked at the imaging studies done in set of patients who were operated on for posterior fossa tumours, and subsequently developed posterior fossa syndrome, and at controls that underwent surgery and did not develop posterior fossa syndrome in an attempt to identify radiological features of posterior fossa syndrome. (47) They found that pre-operatively, there was no difference between the two groups in terms of tumour size, peri-lesional oedema or hydrocephalus. However, brainstem invasion was shown to be statistically significant, as was cerebello-medullary angle involvement. Among post-operative images, middle and superior cerebellar peduncle oedema among those with cerebellar mutism was found to be statistically significant. A 1 year post-operative MRI in this cohort showed those who had had cerebellar mutism to have more significant gliosis or atrophy of total cerebellum, vermis and brainstem. Mean IQ was 16 points lower in patients with cerebellar mutism as well at the end of a 1 year period, showing long standing neurological sequelae.

Long term follow up of children with cerebellar mutism by Robertson et al showed that they had problems in solving novel situations, decreased speed of speech, processing, and reasoning as well as decreased verbal initiation and significantly poor performance in reading, spelling, math, and working memory(48). All of these can affect schooling in the future. Pharmacological therapy for posterior fossa syndrome has been attempted without much success, and counselling of parents as well as children is essential, to teach them compensatory strategies in order to decrease sequelae and the duration of disabilities.

Other post-operative complications

The other common post-operative complications are meningitis (septic as well as aseptic), CSF leak and pseudomeningocoele as shown by Muzumdar et al.(23) Appropriate antibiotics and drainage procedures are advocated for the same. Gopalakrishnan et al did a study on factors necessitating post-op CSF diversion techniques and found that those who had a midline tumour, shorter duration of symptoms at the time of presentation (indicating more aggressive tumour), intra-operative EVD placement and post-operative meningitis/pseudomeningocoele had a higher chance of needing a post op CSF diversion surgery.(49) Hyponatremia following surgery was studied by Williams et al, and was found to be common among those who had obstructive hydrocephalus, and among younger children.(50) Symptomatic hyponatremia was not uncommon, and was associated with increased neurocognitive sequelae later on according to this study.(51)

Radiotherapy

Radiotherapy forms an integral part of adjuvant therapy for medulloblastoma. However, radiotherapy, especially when given to an immature developing brain, often leaves behind

significant sequelae. Hence most protocols try to avoid radiation in those younger than 3 years of age according to the guidelines offered by Lafay Cousin et al.(36) This may vary according to the various protocols used, with HITKK92 not using RT at all, and relying on surgery, aggressive chemotherapy and second look surgery if needed, whereas Headstart I and SFOP guidelines advocate only salvage RT. According to Headstart II guidelines, RT is given only after 6 years of age, or for residual disease. All these measures indicate the awareness that has come regarding neurocognitive sequelae of radiotherapy to a young brain.

Geyer et al studied the effect of high dose chemotherapy alone, without the use of radiotherapy in infants with medulloblastoma and got survival results comparable with regimens which used radiotherapy, with less sequelae.(52) Oyharcabal- Bourden et al studied the effect of reduced dose radiotherapy and standard chemotherapy in children with standard risk medulloblastoma, and found comparable results with those who received full dose of radiotherapy, thereby implying that for this low risk/standard risk disease, radiotherapy can be decreased within acceptable limits.(22)

Radiotherapy for medulloblastoma involves two main areas- one is the tumour bed, and the other being craniospinal irradiation. On an average, the tumour bed site is given around 54 Gy of radiation, within a radius of 1-2 cm of the primary tumour bed. Craniospinal irradiation delivers another 23.4-36 Gy of irradiation to the neuraxis according to Pollack et al.(41) These high doses of radiation result in neurocognitive deficits in the treated children as shown by Robinson et al, with younger children and those receiving higher doses of radiation having a higher chance of developing the same. This is the rationale for avoiding radiotherapy in those younger than 3 years.

Studies by Oyharcabal- Bourden et al etc have looked at stepping down treatment for standard risk medulloblastoma with reduction in radiotherapy in an attempt to decrease the long term sequelae of the aggressive treatment involved for medulloblastoma. The researchers in the above study had concluded that should staging for prognostication be carried out promptly and precisely, then reduced radiation can be used successfully for treatment of standard risk medulloblastoma.(22)

Adjuvant chemotherapy

Adjuvant chemotherapy forms a vital part of the treatment of medulloblastoma. Most regimes use concurrent vincristine weekly with radiotherapy, and thereafter chemotherapy for another 6-8 cycles. Common chemotherapeutic drugs used include vincristine, lomustin, cisplatin, carboplatin, procarbazine, cyclophosphamide and etoposide. Many regimes have now included G-CSF as part of the regime in view of significant cytopenias induced by the chemotherapy, as shown by Geyer et al.(52) Regimens used in the past include the infamous " 8 drugs in a day" regimen, which had intolerable side effects as shown by Oyharcabal Bourden et al.(22)

Chemotherapy adds on further morbidity in the long run, in the form of hearing loss, renal tubular dysfunction, etc, which will be described under late effects. Monitoring for drug toxicities, therefore form an integral part of all chemotherapy with strict monitoring of white cell counts, renal functions, hearing, electrolyte status etc during as well as between chemotherapy cycles, with appropriate management of any imbalance promptly to avoid any untoward events. Chemotherapy regimens as well as drugs are changed if toxicity is too high with the current regimen.

Late effects of treatment

Surgery, radiotherapy as well as chemotherapy have associated long term morbidity. Extensive resection leads to posterior fossa syndrome as described by Doxey et al, with residual neurological deficits as described by Wells et al(45)(47).The use of various CSF shunts as well have their own associated complications, such as shunt infections, shunt malfunction and the possibility of extra- neuraxial metastases as elaborated by Gopalakrishnan et al, and Schweitzer et al(49)(43).

Craniospinal irradiation is associated with neurocognitive deficits and long term neuro-endocrine sequelae. Christopherson et al looked at the late toxicity in 53 patients who had been treated for medulloblastoma, 41% of the survivors had grade 3 or more toxicity as per the NCI common Terminology Criteria for Adverse Events, Version 4.0. These included hearing deficit requiring intervention in 20.5% and cognitive impairment prohibiting independent living in 18%. 4/53 developed secondary malignancies and 3/53 died from treatment related complications severe cerebral oedema, radionecrosis and fatal secondary malignancy. (53)

Knight et al looked at the working memory in children with medulloblastoma. 167 children were included in the study and serial assessments of working memory were done at predetermined time points for 5 years. They found a statistically significant decrease in the age standardized scores, and posterior fossa syndrome was consistently associated with a poorer working memory. Younger age and higher treatment intensity were associated with a greater negative change in working memory. (54)

Younger children may sustain more severe damage due to the immaturity of the brain at the time of irradiation. There is decline in intellectual ability, with difficulty in motor tasks,

perceptual abilities, memory, executive functions as well as verbal ability. In a study of brain tumour survivors who were treated with radiation, done by Packer et al in 2001, in comparison to their disease free siblings, survivors of brain tumours had more significant sequelae. There was a relative risk of 17.5 of developing hearing difficulty, and 49% reported having difficulty with co-ordination and 26 % reported difficulty with motor skills. Seizure disorder was present in 25 % of the survivors(55). In yet another study by Ris et al, 43 children who had undergone treatment for medulloblastoma with reduced dose of RT and adjuvant chemotherapy were evaluated longitudinally for cognitive functioning. According to this study, there was a decline in the domains of Full Scale Intelligence Quotient (FSIQ), Verbal IQ (VIQ) and non-verbal IQ (NVIQ), by -4.3, -4.2 and -4.0 points respectively per year. Those who are younger than 7 years at the time of radiation had a more significant decline in NVIQ, and females had a statistically significant decline in VIQ when compared to males. It was also shown that those who had a higher baseline IQ had more of a decline as well. (56)

Robinson et al, while looking at the neuro-cognitive sequelae of posterior fossa paediatric tumours, found significant deficits in the indices of neuro-cognitive functions such as overall cognitive functioning, academic achievement, attention/concentration, executive function, information processing speed, psychomotor skills, verbal memory, visuo-spatial skills, visuo-spatial memory and language. (57) This indicates that the deficits are encompassing than thought previously, and cognitive assessment, follow up and appropriate training and rehabilitation might be necessary for all survivors of childhood brain tumours.

Knight et al also looked at the hearing disabilities acquired as a result of cisplatin toxicity. Factors increasing the risk for cisplatin ototoxicity include a cumulative cisplatin dose of 360

mg/m2 or greater, associated renal dysfunction, and use of other ototoxic medications during treatment such as loop diuretics, aminoglycoside antibiotics, carboplatin etc. (58) Cranial irradiation before cisplatin therapy also increases risk of hearing loss.

Cisplatin toxicity typically starts at high frequency levels, and progresses to involve lower frequencies as well. Tinnitus may be found in association with the hearing loss. Hearing loss usually begins after the 3rd cycle of chemotherapy according to Knight et al, hence hearing screening has accordingly been incorporated into most protocols after the third cycle. But what was most striking from this study was that the hearing loss can progress even after completion of therapy. Therefore periodic monitoring is required after completion of treatment during follow up visits as well.

Brock et al studied the effects of platinum based chemotherapeutic agents, i.e, cisplatin and carboplatin on hearing.(59) Based on these studies, oto-protective measures, such as reduction of total dose of drugs, and gradual escalation of doses have been planned for all regimens using these drugs, however these may affect the efficacy of the drug with regard to the tumour. The SIOP guidelines for ototoxicity classify hearing loss due to drugs as given below:

Table No. 4: SIOP ototoxicity scale

SIOP Boston Ototoxicity Scale Grade	**Parameters**
0	<20 dB HL at all frequencies
1	> 20 dB HL (i.e., 25 dB HL or greater) SNHL above 4,000 Hz (i.e., 6or 8 kHz)
2	>20 dB HL SNHL at 4,000 Hz and above
3	>20 dB HL SNHL at 2,000 Hz or 3,000 Hz and above
4	>40 dB HL (i.e., 45 dB HL or more) SNHL at 2,000 Hz and above

This scale is more functional and predicts the need for hearing aids and special training, as opposed to the conventional measures of hearing loss. Brock et al also advocates the use of anti-oxidants such as NAC which protect against the ototoxic effects of the drugs, and do not decrease their efficacy on the tumours.(59) The other drugs under consideration as otoprotectors as STS, a thiol reducing substance, amifostine, D-methionine and ebselen. However, none of these have been approved for human use yet.

Knight et al states that the impact of hearing loss depends on the child's age, the severity of the hearing loss and affected frequency range, the timing of intervention, and other factors.(58) Speech and language development may be affected when hearing loss is acquired in early childhood. Older children and adolescents are at risk for reduced

educational achievement, social isolation, emotional difficulties, and decrease in health-related quality of life.

Guillaume et al also found a statistically significant association between CSF shunting and hearing loss. They found that age, side of shunt, evidence of CNS dissemination, diameter of cochlear aqueduct, and treatment protocol did not have a significant effect on shunt-related ototoxicity.(60) This is thought to be as a result of increased ICP prior to shunt surgery, as changes in CSF pressure is thought to have an effect on cochlear physiology via endolymph expansion in the setting of a patent cochlear aqueduct.

Arany et al and Yiao et al have shown the nephrotoxic effects of cisplatin in addition to its ototoxicity. (61)(62) The toxic effects of cisplatin are mainly evident on the tubules, and can be minimised by following the set guidelines- adequate prehydration, and maximum infusion for 24 hours. Longer duration of infusion has been shown by Arany et al to have an association with increased toxicity.(61) Studies by Erdlenburgh et al have also drawn similar conclusions(63). These renal effects can be transient causing derangement of renal parameters and electrolyte imbalance, or can be long-standing.

Vincristine, another chemotherapeutic drug which is commonly used in treatment of medulloblastoma, has been long known to have associated neurotoxicity as a predominant side-effect. Gomber et al studied the neurotoxic effect of vincristine on Indian children and found that up to 50 % of Indian children treated with vincristine had side-effects, which is much higher than the rates reported from western studies.(64) Legha et al have shown that vincristine causes peripheral neuropathy, autonomic neuropathy and cranial nerve palsies in

addition to being life-threatening if administered intrathecally. This study also showed that liver dysfunction and pre-existing neurological dysfunction can worsen this.(65)

Gomber et al showed that though clinical improvement in the peripheral neuropathy may occur within the first few weeks, electrophysiological changes persist beyond 6 months and more, predicting that the effects are longer lasting than previously thought.(64)

The endocrine effects of treatment include hypothyroidism, growth hormone deficiency, delayed puberty and SIADH. Gurney et al found that growth hormone deficiency is seen in almost all peripubertal children and upto 50% of all children treated with whole brain RT for medulloblastoma, with a relative risk of 277.8 when compared to healthy peers, with a relative risk of 86.1 with respect to growth hormone requirement for inducing puberty. (66)Ilveskoski et al studied growth impairment and effects of growth hormone supplementation in children who had been treated for central nervous system tumours. The results of this study showed the most marked loss of height velocity among those children who received craniospinal irradiation in addition to chemotherapy. (67) However, what was striking was that even those who hadn't had any radiation to the hypothalamo-pituitary axis also had growth retardation. Response to growth hormone therapy was impaired in those who had reached pubertal age, as compared to those who were prepubertal at the time of administration of growth hormone. This shows that growth monitoring is mandatory in all children treated with radiotherapy for medulloblastoma and growth hormone supplementation is often necessary.

Hypothyroidism occurs as a result of radiation to the hypothalamic area as well as scatter radiation received by the thyroid during radiotherapy. Gurney et al showed that there is a

relative risk of 14.3 for developing hypothyroidism among survivors of childhood brain tumours when compared to their siblings.(66) Life-long thyroxine supplementation with frequent monitoring is warranted to prevent the consequences of hypothyroidism.Brandes et al reviewed the incidence of endocrine dysfunction among those treated for brain tumours, and advised screening for the following four main categories- GH deficiency, gonadal alteration, hypothyroidism and hyperprolactinemia(68). Routine screening for the above and prompt pharmacological therapy will remedy the undue and preventable effects of these endocrine dysfunctions.

Alterations in sodium metabolism in the form of SIADH, cerebral salt wasting and diabetes insipidus occur as a consequence of surgery and radiotherapy. Williams et al studied the incidence of post-operative hyponatremia and any identifiable risk factors for the same. It was found that approximately 12 % of those who underwent surgery had hyponatremia as defined as serum sodium <130 mmol/l. Hyponatremia was symptomatic in most children with 21% having seizures, and 41% presenting with altered sensorium(50). Younger age at presentation and obstructive hydrocephalus were identified as two major risk factors for symptomatic hyponatremia by this study. It was also noticed that these children had a longer, more complicated hospital stay and a 6-fold increase in moderate to severe disability when compared with those who were matched for age and tumour location, without any hyponatremia.(51)

In the latter part of treatment, cerebral salt wasting has been reported as a common cause for hyponatremia. Cerebral salt wasting usually subsided within 2-4 weeks according to studies by Papadimitriou et al, with appropriate supplementation of fludrocortisone.(69)

Carrascosa et al also advocate workup for hypothyroidism, mineralocorticoid deficiency and hypophyseal/ pituitary dysfunction in the presence of difficult-to-treat hyponatremia in CNS tumour survivors as these endocrine conditions are commonly seen in these children.(70) SIADH, another common cause for hyponatremia in children post treatment for CNS tumours, warrants fluid restriction and desmopressin supplementation. The supervision of a paediatric endocrinologist for treatment of the above is advocated.

Multiple cardiovascular complications have also been noticed in the post-treatment period of CNS tumours. Gurney et al studied the incidence of cardiovascular complications among those who had been treated for CNS tumours. There was a 40-fold increased risk of stroke among CNS tumour survivors when compared to their siblings. However there was no increased risk of arrhythmia and only a two-fold increase in the risk for angina when compared to their siblings according to this study. (66)Among the cases, those who underwent both chemotherapy and radiotherapy were three times as likely to have a stroke when compared to those who had only radiotherapy.

Bowers et al also confirmed the increased risk of stroke among childhood CNS tumour survivors in their study(71). Diller et al, in their study on chronic diseases found that not only was there an increase in endocrine diseases such as hypothyroidism, growth hormone deficiency and disorders of puberty, female survivors of CNS tumours were also more likely to develop obesity, especially if they were younger at the time of diagnosis and had received RT to the hypothalamic area.(72) This study also found an increase in cardiovascular events and neurological and neurosensory deficits.

Neglia et al from the Childhood Cancer Survivor group reported that new CNS tumours can occur following treatment for CNS malignancies.(73) Gliomas and meningiomas were the commonest tumours found in this study, with gliomas occurring after a mean of 9 years after diagnosis, and meningiomas after an average of 17 years. Radiation exposure was found to be a significant risk factor for development of subsequent neoplasms in this study.

Strodtbeck et al also studied the risk of subsequent cancer following primary CNS tumours, and found that the tumour with the highest risk of a second malignancy was medulloblastoma/ PNET, with a relative risk of 4.31 when compared to 1.26 for all CNS tumours. (74)In addition to CNS tumours, tumours of the thyroid, GIT and bone have also been reported after completion of treatment for medulloblastoma according to this study. Leukaemias are another late event following treatment for medulloblastoma/PNET, thought the incidence is less compared to the other solid tumours.

Lew et al studied the incidence of cavernomas secondary to radiation among the survivors of medulloblastoma. (75)31 % of the patients studied in this study developed cavernomas (imaging and histology proven). The incidence increased progressively with time. No significant correlation between gender, age at diagnosis, dose of radiation received or the source of radiation, and the risk of development of cavernoma was noticed. These lesions were found to have a benign course however, and did not need aggressive treatment**.**

Prognosis and recurrence

Over the last few decades, there has been a drastic improvement in the survival rates of children with medulloblastoma. This has been attributed to improved and early diagnosis, improved treatment modalities and surveillance. However, it is well-known that survival

rates depend on multiple factors, of which the current impetus is on favourable molecular subgroups. The National Cancer Institute (US) gives the prognosis according to age groups- among children more than 3 years of age with average risk, 5 year event free survival rate is up to 80%.

Those with high risk disease who were more than 3 years at the time of diagnosis had a 50-60 % survival rate according to this study. Infants with desmoplastic variant have upto 75 % survival rates with current treatment regimens, however there is only 40% survival rates among those with disseminated disease and among those who were less than 3 years at the time of diagnosis. Packer et al gave the 5-year disease-free survival rates to be 50% to 60% in patients with average-risk disease and 40% or less in patients with high-risk disease in the 1990s.(76) However, in the last decade, the trend has changed and Packer et al, in their mor recent study have shown that among children with non-disseminated disease who were treated according to standard protocol with chemotherapy and radiotherapy, five- and 10-year event-free survival rates were 81+/-2% and 75.8+/-2.3% respectively and overall survivals were 87+/-1.8% and 81.3+/-2.1%.(77)The chemotherapeutic regime, sex, race, gender or age at diagnosis did not have any impact on the event free survival rates. Of the seven patients in this cohort who relapsed after 5 years, 4 had local relapse, 2 had local plus supratentorial disease, and 1 had supratentorial disease alone. Fifteen patients developed secondary tumours as a first event at a median time of 5.8 years after diagnosis. All non-CNS solid secondary tumours occurred in regions that had received radiation. This studied showed the cumulative 10-year incidence rate of secondary malignancies to be 4.2% (1.9%–6.5%). It also concluded that few patients with medulloblastoma will relapse ≥5 years post-diagnosis, and that relapse will occur predominantly at the site of the primary tumour.

Rutkowski et al studied the prognosis of medulloblastoma treated between the years 1987-2004, among the various histological subgroups and found that 8-year event-free survival (EFS) and overall survival (OS) were 55% and 76%, respectively, among those with desmoplastic/nodular medulloblastoma or medulloblastoma with extensive nodularity. (78)These rates came down significantly to 27% and 42%, respectively for children with classic medulloblastoma. In children with large cell anaplastic medulloblastoma, the same rates were a dismal 14% and 14%. These values were statistically significant, as far as prognosis in relation to histology was concerned.

Raleigh et al showed how the molecular subgroups played a major role in determining the prognosis of medulloblastoma.(25) This study gives the survival rates to be approximately 95%, 60-80%, 40-50% and 75% for WNT, SHH, group3 and Group 4 respectively. This wide variation clearly illustrates the major role played by molecular subgrouping in prognosis of medulloblastoma.

Quality of Life (QOL)

As shown above, with current therapy, event free survival rates for average risk medulloblastoma is 75-80%. However these survivors have significant late effects of therapy which are likely to affect their quality of life. These include medical problems such as hypothyroidism, hyponatremia, pan-hypopituitarism, etc, in addition to hearing loss, cognitive difficulties, etc as described before. Brinkman et al in their studies found an increase in suicidal ideation among survivors of paediatric brain tumours.(79) Mulhern et al also found significant cognitive difficulties among survivors of brain tumours, with younger

children, higher radiation exposure and female sex being significant risk factors for more rapid decline in cognition. (80)

Maddrey et al studied the cognition, functional outcome and quality of life of medulloblastoma survivors in the second decade after treatment.(81) They found that there was significant impairment in all domains, including attention, memory, visuo-spatial abilities, motor functioning, language, and executive functioning. Significant impairments were also present in all psychosocial domains examined, including employment, ability to drive an automobile, participation in normal education, independent living, and dating and interaction. What was most interesting in this study, however, was that the quality of life scores, as reported by both survivors and their caretakers, were within the normal range. This indicates that though survivors of childhood medulloblastoma have significant deficits in a wide-range of neuropsychological functional domains, the survivors and their families do not report an impaired quality of life.

Johnson et al had also studied the quality of life of survivors and found similar data, with none of the survivors scoring more than 90 on Intelligence Quotient assessment, and 78 % of the respondents having some degree of learning disabilities(82). These studies show the effects of therapy for medulloblastoma on the cognition and quality of life of survivors, and advocate reduction of radiotherapy where feasible.

Frange et al assessed the outcome of medulloblastoma survivors in multiple domains using self-reported questionnaires using Health Utility Index.(83) At a median follow up duration of 14.4 years from the time of diagnosis, this study found frequent late sequelae including neurological impairment and endocrine dysfunction. Psychosocial functioning was also

impaired in the majority of survivors. None of the males in the study had children, and only three of the females had offspring, thereby raising the possibility that the alkylating agents used for chemotherapy might be responsible for infertility among survivors as well. Female survivors had less difficulty socialising as compared to the male survivors. Early intervention might be helpful in decreasing the neurocognitive sequelae among survivors.

Instruments to measure QOL need to be multidimensional, assessing physical, mental, social and psychological aspects of well-being. Paediatric Quality of life inventory (peds QL) has been widely used to assess health related QOL in children It assesses 4 main areas – physical function, social, emotional and social or work domains. This test was used by Kulkarni et al for assessment of quality of life of long term survivors of posterior fossa brain tumors, which showed that there was no significant decline in quality of life of survivors unless they had residual hydrocephalus or were from a poor socio-economic status.(84)

We have used PedsQl as a tool for studying the quality of life of survivors, as it is a validated tool for assessment among brain tumour survivors.

Justification for this study

Medulloblastoma is the second most common childhood brain tumour. In this study, we looked at the clinical profile and outcome of children with medulloblastoma treated in our unit and compared the same with published literature.

Our study looked at molecular subtypes of medulloblastoma seen in our patient population and compared it with clinical profile and outcome. This data was also compared with other studies.

Quality of life of children with medulloblastoma is compromised due to morbidity from the disease itself as well as complications of treatment as mentioned above. In our joint clinic with multidisciplinary team, many of these issues were identified and managed on a regular basis. During this study, we compiled all the information related to this. QOL assessment was done using a standard Peds QL tool from MAPI organization. This tool assesses QOL in four domains, namely physical, social, and emotional and work related functioning. Permission for using this tool was obtained from the organisation (copy of which is attached among the annexures). We hope that this study will help in better understanding and management of medulloblastoma, minimising the late sequelae and maximising the quality of life of medulloblastoma patients in the future.

METHODOLOGY

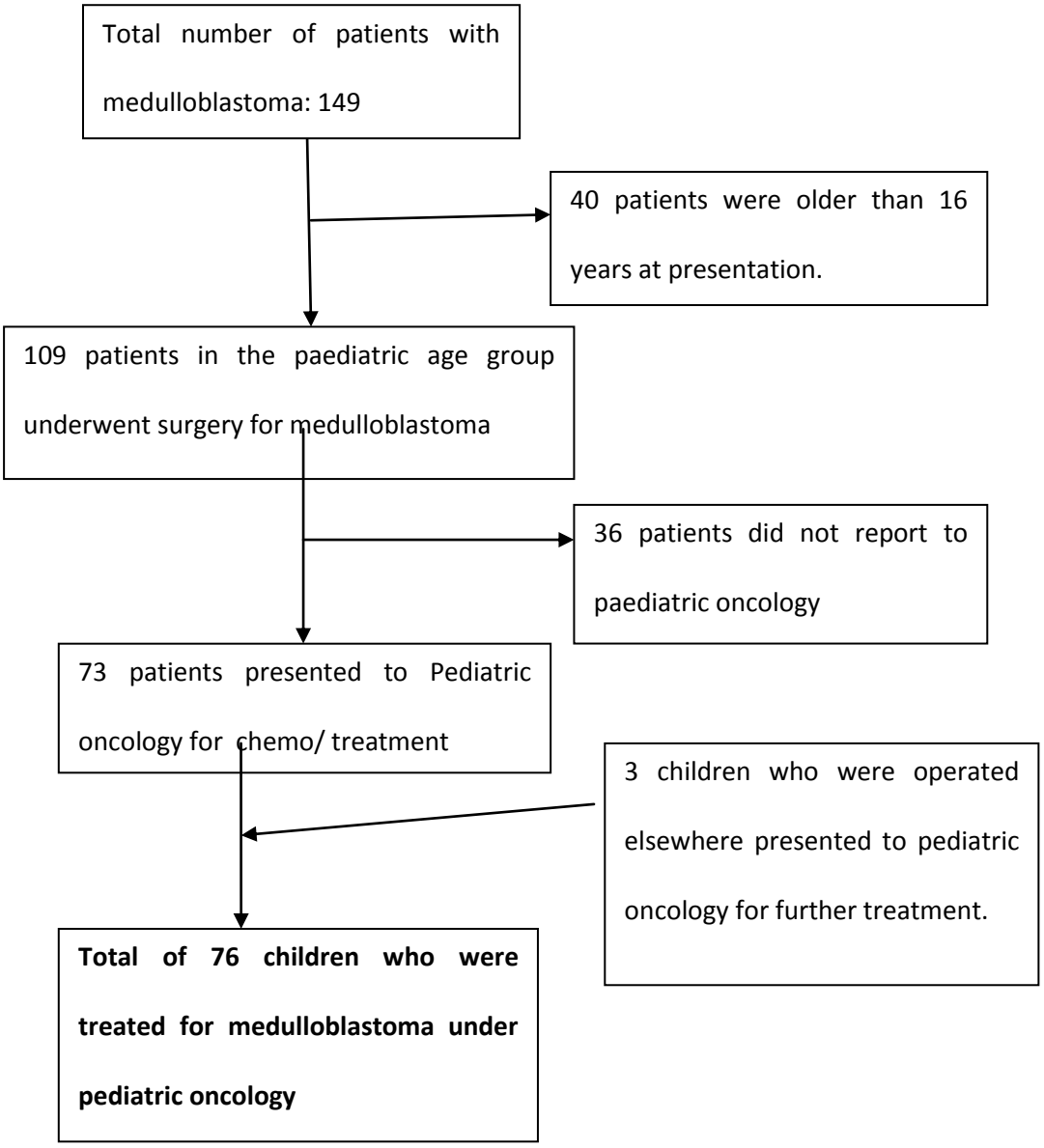
This study was carried out among the patients who attended the paediatric haematology-oncology unit of the tertiary care hospital where the primary investigator was doing her postgraduate training. The study included patients who had presented to the hematology-oncology department for treatment of medulloblastoma between the years 2004-2014. The institutional review board approval was sought for and received prior to commencement of the study. (Please see the annexures for the copy of the same).

There were a total of 149 patients who were diagnosed with medulloblastoma between the years 2004-2014 based on biopsy. Of these, 109 were paediatric medulloblastoma and the rest were in the adult age group. Among these 109 paediatric medulloblastoma patients, 73 sought treatment in paediatric hematology-oncology unit, the rest were lost to follow up to RT and oncology, and took surgical treatment alone. In addition to these 73 patients, 3 patients whose primary surgery had been performed elsewhere also presented to the haematology-oncology department for further management. Hence, a total of 76 patients were included in the study for the purposes of clinical profile.

Among these 76, 50 completed treatment and 10 of them died of recurrence after completion of treatment. Of the remaining 40, five were lost to follow up after completion of treatment and being in remission for a few years and 2 had recurrence of tumour hence was sent home on palliative treatment. Quality of analysis has been done for 33 of the 35 who were contactable for administering the QOL questionnaire.

Tumour immunohistochemistry was done for 43 of these 76 patients. Beta catenin was the marker that was used, with nuclear positivity categorising the tumour as WNT. Of the

remaining tumours which were negative for nuclear beta catenin, those with desmoplastic/ medulloblastoma with extensive nodularity histology were categorised as Sonic Hedgehog category, whereas the remaining were taken to be non WNT/ non SHH.



Clinical profile was derived by retrospective chart analysis. The patients' treatment records, operation notes, radiology data available for the last 10 years, chemotherapy protocols and follow up data in OPD charts were utilised for the same. The late effects of therapy, such as endocrine dysfunction, cognitive impairment, hearing defects, etc were also looked at.

Tumour immunohistochemistry were carried out on tissue samples from the tumours which were already available in the pathology department from the surgeries which were done over the last 10 years. Beta catenin was the marker which was used. In addition to this, histology was verified by a senior neuropathologist to confirm the same and to classify the ones which were negative for nuclear beta catenin into SHH and non WNT/ non SHH group. Further studies were carried out based on the same.

Quality of life of the survivors was assessed using PedsQL, which is a validated tool for assessment of quality of life of brain tumour survivors in the following domains-physical, social, emotional and school functioning. Permission was sought from and received from the mapi organisation, which owns the copyright for this questionnaire (please see the annexures for a copy of the permission letter). Questionnaires were translated into languages which were easy for the patients and the parents to understand, and were administered by the principal investigator herself to the patients, either in person or over the phone after obtaining informed consent. The patients and parents were also given a patient information sheet for clarifying their doubts prior to participation, making it clear that participation was absolutely voluntary.

The results were transcribed onto Microsoft XL sheets after the data was collected. The data analysis was done using SPSS version 16.0.

RESULTS

There were 149 patients with medulloblastoma who presented to the neurosurgery department of this institute between the years 2004 to 2014. Patients older than 16 years (40 patients) were at the time of diagnosis were excluded from this study.

Of the 109 paediatric patients with medulloblastoma, only 73 came to the paediatric haematology-oncology unit for further treatment, the remaining 36 were lost to follow up after surgery. Three children with biopsy proven medulloblastoma, who had been operated elsewhere, were also included as they took post-operative treatment in our unit. The study population therefore includes a total of 76 paediatric medulloblastoma patients who were seen in the Department of Paediatric Haemato-oncology unit in this tertiary care centre in South India between the years 2004 and 2014 March.

Clinical profile of patient population

Among the entire paediatric medulloblastoma population seen in this institute (112 patients, 109 operated here and 3 operated elsewhere), there were 75 males as against 37 females, making the male to female ratio 2:1.The gender ratio among the 76 who reported to our unit, was 1.8:1 (49 boys and 27 girls)

Gender distribution of study population: (n=76)

Table No. 1: Gender distribution of the study population

	Frequency	Percent
Male	49	**65**
Female	27	**35**
Total	76	**100**

There was a male preponderance, with a male: female ratio of 1.8:1.

Age at presentation (n=76):

The age at presentation in this study population varied from 1 year to 15 years. The mean age at presentation was 8.49 with a standard deviation of +/-3.45. The following table represents the different age groups into which our patients belonged.

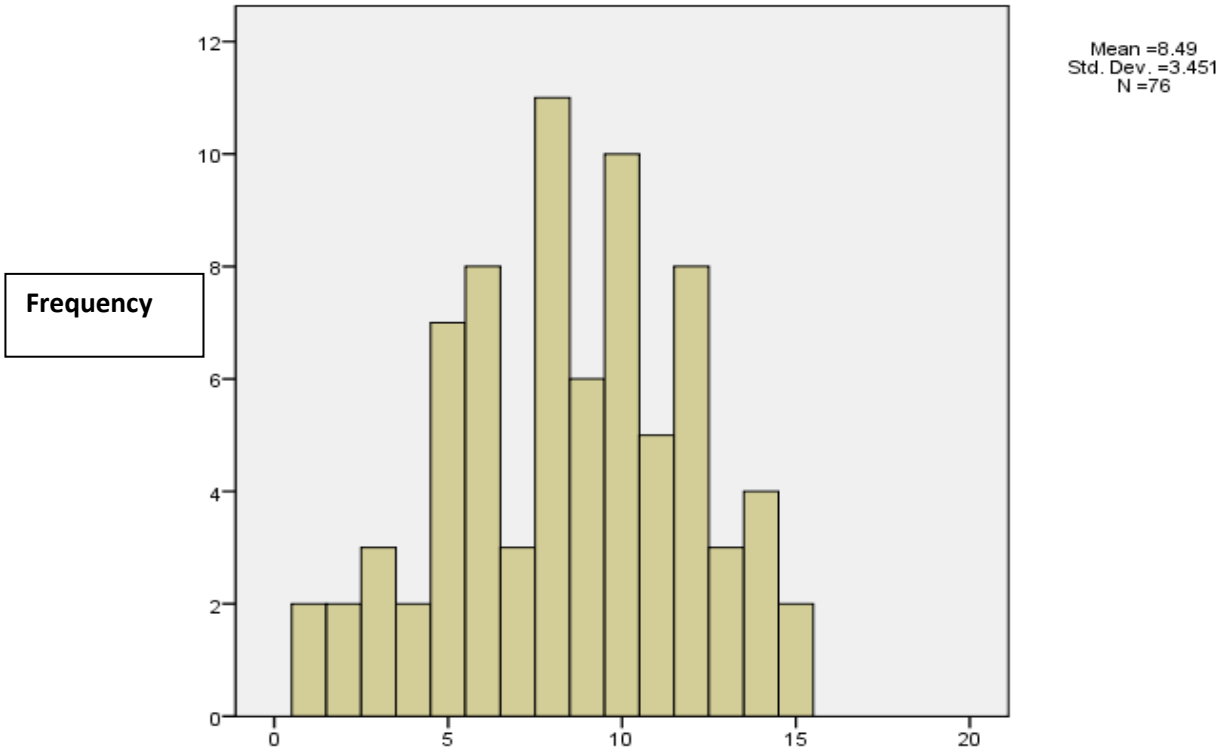
Table No. 2: Age distribution of children at diagnosis (n=76)

Age group	**Frequency**	**Percentage**
<=3 years	7	9%
4-7 years	20	26%
8-10 years	27	36%
>10 years	22	29%

As depicted in the above table, the study population had only 7 patients in the age group that was younger than 3 years. The majority of patients were in the age group 8-10 years,

closely followed by those who were more than 10 years. The histogram given below represents the age distribution of the study population.

Figure No.1: Age at diagnosis for the patient population (in years)



The histogram depicts how most of the cases were clustered around 8-10 years of age, with a few outliers who were less than 3 years and more than 13 years respectively at both ends of the age distribution.

<u>Symptoms at the time of presentation (n=76):</u>

The various symptoms with which our patients had presented were looked at. The predominant symptoms were headache, vomiting, ataxia and visual disturbances.

The table below gives the details of the symptoms at presentation in our study group.

Table No. 3: Symptoms of patients with medulloblastoma at the time of presentation (n=76)

Symptom	Frequency	Percentage
Headache	65	86%
Vomiting	60	79%
Ataxia	44	58%
Blurring of vision	12	16%
Increase in head size	3	4%
Giddiness	3	4%
Tinnitus	3	4%
Tremors	1	1%
Seizures	1	1%

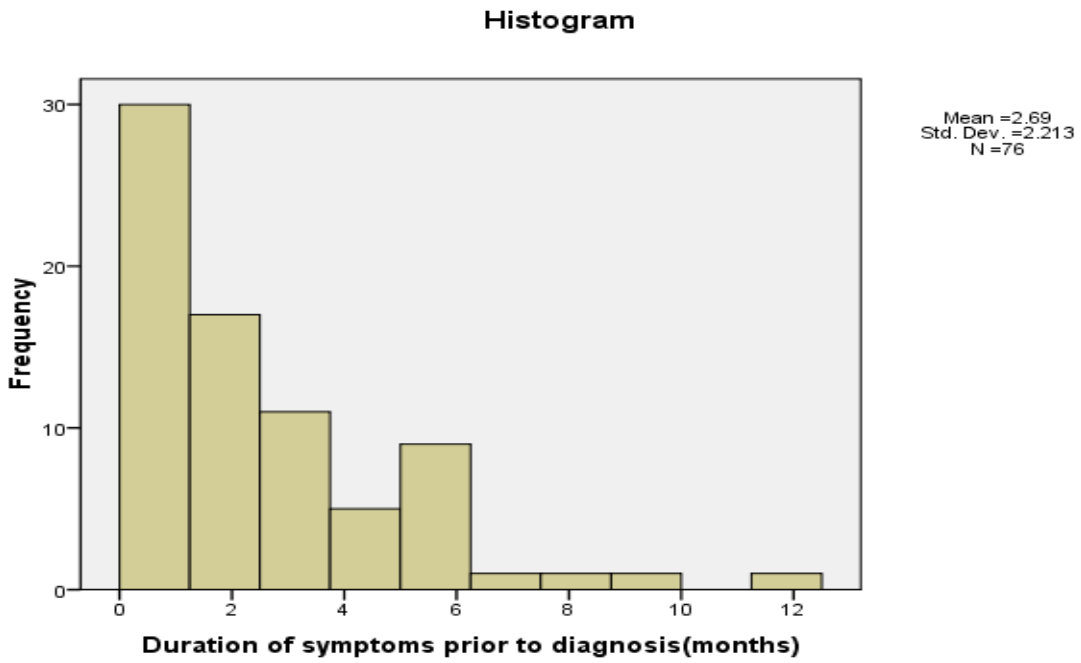
These symptoms are either as a result of raised intracranial tension (headache, vomiting, visual disturbances) due to obstruction to the CSF pathway as a result of the classic midline fourth ventricular location of the tumour, or due to the cerebellar involvement due to cerebellar location of the tumour or due to pressure effects(ataxia, tremors, giddiness). In our study population, increase in head size was also reported as a presenting symptom in 3 children who were less than 2 years at the time of presentation. Tinnitus was seen mainly in those who had cerebellopontine tumours, as a result of compression of the VIII th cranial nerve as a result of the location of the tumour.

Duration of symptoms prior to presentation (n=76):

The duration of symptoms prior to presentation to this hospital for further management was analysed. The mean duration was 2.69 months +/- 2.21.

This data is represented in the histogram given below:

Figure No.2: Duration of symptoms prior to presentation



It was seen that 59 patients (78%) presented within 3 months of onset of symptoms. For another 13 children (17%), it took between 4-6 months from the time of onset of symptoms for a diagnosis to be made whereas 4 out of 76 (5% of the total study population) had a diagnosis made only after 6 months of onset of symptoms.

Surgical Treatment and complications

Emergency pre -op CSF diversion procedures

Symptoms of raised intracranial tension were one of the most important reasons for seeking medical attention. This also meant that some of them had impending herniation, which was life-threatening, at the time of presentation itself. These patients were taken up for

emergency CSF diversion procedures. The proportion of patients who underwent shunt surgery prior to definitive surgery was looked at. 22 of the 76 patients (29 %) had required a preliminary shunt surgery, either at this centre or elsewhere. The various shunt procedures used were ventriculoperitoneal shunt in 18 of the 22 (82%), extraventricular drainage in 2 children (9%) and ventriculostomy in two children (9 %)

The remaining patients could be managed successfully with steroids and other ant-oedema measures.

Post-op CSF diversion procedure (n=76)

13 patients had ventriculoperitoneal shunts placed for CSF drainage post-operatively. This was in addition to the 22 patients who had had shunts pre-operatively, making the total number of patients needing CSF diversion procedures in this series 35. This was indicative of the fact that in some patients, tumour resection to the safest extent possible might not be sufficient for adequate CSF drainage, as shown by Muzumdar et al. These patients did well after placement of a CSF shunt, with significant improvement in sensorium. Over shunting of the CSF was seen in 2 of these 35 patients (6%) much later, requiring ligation of the shunt tip.

Surgical resection (n=76)

Surgical resection of the tumour was classified into subtotal or gross total based on extent of residual tumour. Gross total resection of the tumour indicates a post-op residual tumour volume of < 1.5 cm2. Subtotal resection, or residual tumour volume >1.5 cm2 makes the patient fall into high risk category. The completeness of surgical resection at primary surgery was therefore assessed. It was found that only 37 of the 76 patients (49%) had undergone gross resection of the tumour, making the remaining patients high risk disease in view of residual tumour.

Table No. 4: Completion of surgical resection (n=76)

Resection	Freequency	Percentage
Gross total	37	49
Subtotal	39	51
Total	76	100.0

Residual disease post-operatively (n=76):

The post-operative scans were analysed to look for residual disease. 48 of the 76 (64 %) had radiological evidence of residual disease on the post-operative scans. Of these, 30(39%) were more than 1.5 cm2 in size, qualifying them as high risk disease according to the risk stratification method advocated by Packer et al.

Correlation between surgical excision and residual tumour: The correlation between the degree of surgical excision and the volume of residual tumour was considered. The results obtained were as below:

Table No.5: Correlation between surgical excision and residual tumour (n=76)

	Gross total excision	Subtotal excision
Residual tumour present	13(35%)	34(87%)
Residual tumour absent	24(65%)	5(13%)

Chi square test was done to look at correlation between the two parameters, and the result obtained was 0.23, which was not significant.

Post-operative complications (n=76):

37 out of the 76 patients (49%) had post-operative complications. The most common post-operative complication was meningitis in 24%. However, the most devastating complication was posterior fossa syndrome, which was seen in 14 % of the patients post-operatively.

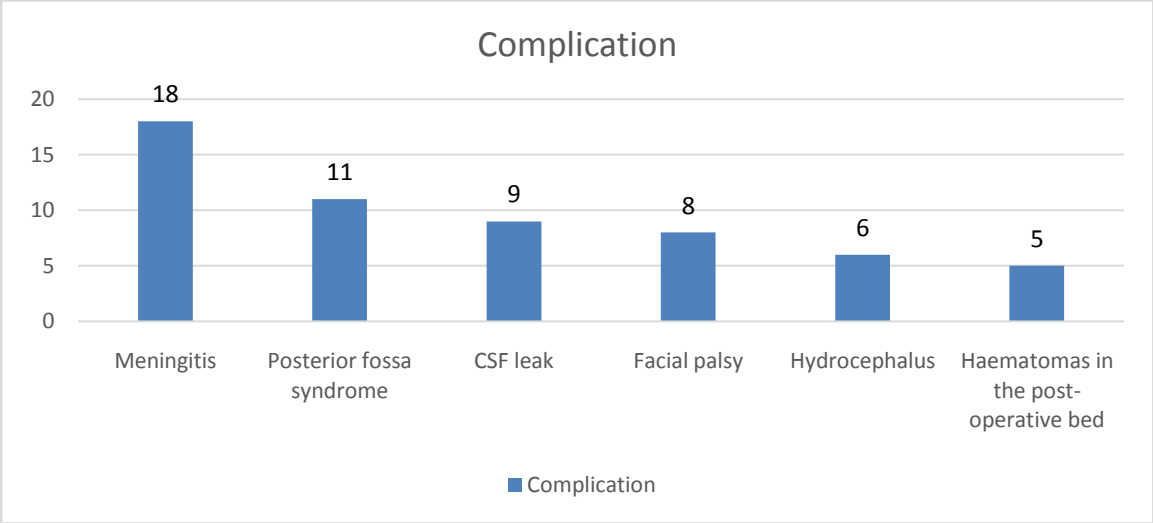
CSF leak was treated conservatively with suturing and antibiotics in most cases. Facial palsy, which was seen in 11 % of the cases, was transient in all children. Haematomas in the post-operative bed were monitored closely in 2 of the 5 and were re-absorbed spontaneously, whereas the remaining 3 needed re-exploration and evacuation of the haematomas due to pressure effects. Hydrocephalus persisting in spite of tumour resection was seen in 6 patients post-operatively, necessitating CSF diversion procedures post-operatively for the same.

The various post-operative complications encountered were the following:

Table No. 6: Post-operative complications

Serial No:	Type of complication	Frequency
1.	Meningitis	18(24%)
2.	Posterior fossa syndrome	11(14%)
3.	CSF leak	9(12%)
4.	Facial palsy	8(11%)
5.	Hydrocephalus	6(8%)
6.	Haematomas in post-op bed	5(7%)

Figure No.3: Post-operative complications:



Post-operative imaging (n=76):

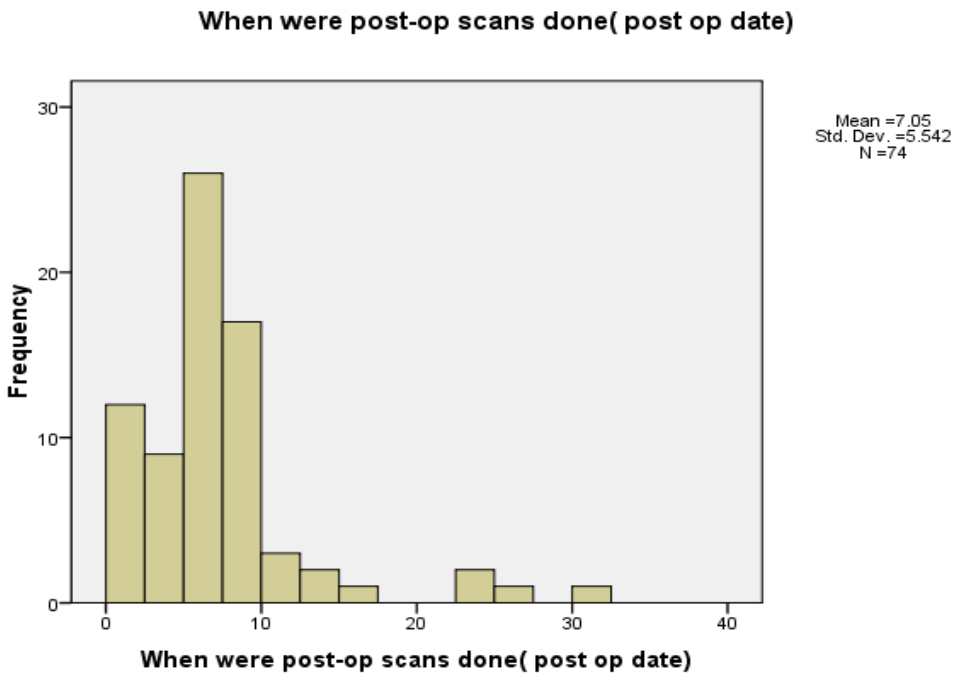
Post-operative imaging modalities used were compared among the 76 patients. 93.4 % had CT scans, whereas 6.6 % had MRI scans post-operatively.

Time interval between surgery and post-operative imaging (n=76):

Post-operative imaging with MRI of the brain is ideally done before 3 days, as shown by Raleigh et al. The reason for this is that after 72 hours, the chances of residual tumour being obscured by granulation tissue which will be formed over the post-operative tumour bed is much higher, thereby preventing proper visualisation of residual tumour. However, in this centre, the current practice is to do a contrast CT in the post-operative period before discharge from the neurosurgical side, irrespective of the duration between surgery and imaging. Since contrast will be able to differentiate between blood and residual tumour, this is thought of as adequate for imaging residual imaging. Interval between surgery and post-operative imaging varies widely among the 76 patients in the study group, from 1 day to 32 days after surgery, with a mean duration of 7.05 days +/-5.53. 14 patients of the

76(18%) had post-operative imaging done before 72 hours and the remaining 62(82%) who had imaging done after 72 hours.

Figure No. 4: Time interval between surgery and post-operative imaging



Staging investigations

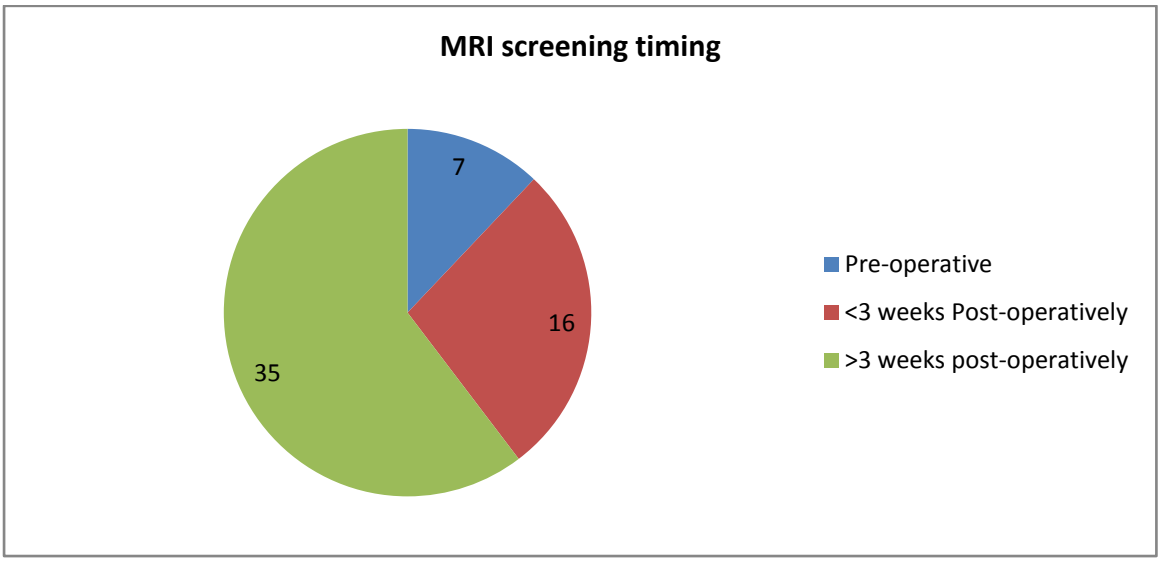
MRI spine for staging (n=58):

Only 58 of the 76 patients (76%) had been screened using MRI of the spine for evidence of leptomeningeal metastases. Of these 58, 23 showed evidence of leptomeningeal metastases (40 %), whereas the remaining 35 were normal.

Like the post-operative screening for residual tumour, MRI spine screening for metastases also has guidelines, which state that MRI spine screening should be done either prior to surgery, or at least 3-4 weeks after surgery. This is to prevent artefacts due to the presence of blood and tissue debris in the CSF circulation in the immediate post-operative period which can lead to clumping of the roots, leading to false positive results, or can obscure the leptomeningeal metastatic deposits leading to false negative results.

In our study population, among the 58 who had MRI screening of the spine done, 7(12%) of them had MRI screening prior to surgical intervention, 35(60%) of them had spine screening more than 21 days after surgery, and 16(28%) had MRI at less than 21 days after surgery. The timing of the imaging was appropriate in 42 (72%) out of 58 patients.

Figure No. 5: MRI spine screening for metastatic workup – timing (n= 58)

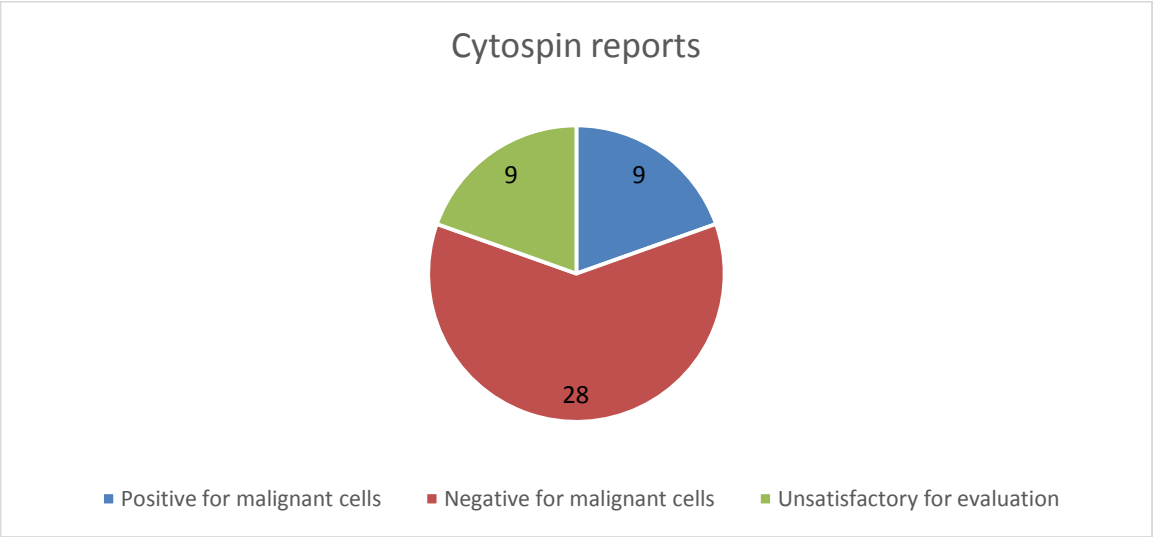


<u>CSF cytology (n=46):</u>

As part of the metastatic workup, CSF cytology was also done. Fouladi et al have advised both MRI spine as well as CSF cytology as part of metastatic workup as their study has shown that there are chances of missing leptomeningeal metastases should either one investigation be done in isolation. 46 of the 76 patients (61%) in this study population had CSF cytology . 39 out of the total 76(51%) had undergone both MRI spine screening as well as CSF cytology as part of metastatic workup.

Among those who underwent CSF cytology, 9 were positive for malignant cells, (20 %), 9 were unsatisfactory for evaluation (20%) and 28 were negative for malignant cells (60%). The results of the cytospin are depicted below:

Figure No. 6: Cytospin for evidence of CSF spread of disease- reports



Overall, 58/76 (76%) had MRI spine and 46/76 (61%) had CSF cytology done for metastatic workup. Only 39/76(51%) had both CSF and MRI spine done. All children had one or the other test done as part of metastatic work up. It was noted that 6 patients whose spine screening had revealed the presence of leptomeningeal metastases had an unsatisfactory CSF cytology, whereas 5 children who had been diagnosed with leptomeningeal metastases based on MRI spine screening had cytology which was negative for malignancy. Similarly, 2 children whose cytology were positive for malignancy had imaging of the spine which was negative for metastatic spread of the disease. CSF cytospin and MRI of the spine were both positive for metastases in 6 children. If CSF cytospin alone had been performed on all the children in this cohort, 11 children with metastases would not have been detected, whereas MRI spine screening alone would have been insufficient for diagnosis of metastases in one child. This shows how combined screening with both CSF cytology as well as MRI is still better than cytology alone or MRI alone. Based on cytology and/or MRI spine screening 27/76 (36%) had metastatic disease.

Surgical procedures for localised versus metastatic disease(n=76)

Surgical procedures for localised disease and metastatic disease were compared. The results obtained were as follows:

Table No.8: Comparison of surgical resection patterns in metastatic and non metastatic disease

	Metastatic disease	**Non metastatic disease**
Gross total resection	13(48%)	35(71%)
Subtotal resection	14(52%)	14(29%)

48% of those with metastatic disease had undergone gross total resection of the tumour, whereas 71% of those with non metastatic disease had undergone gross total resection. Student t test was applied to the above data to look for significance, however the p value obtained was 0.10172, which was not significant.

Residual disease in metastatic disease versus localised disease: (n=76)

Residual disease among those with metastatic disease and those with localised disease was compared. The results are shown below:

Table No.9: Comparison of residual disease in metastatic and localised disease

	Metastatic disease	**Localised disease**
Residual disease present	15(55%)	14(29%)
Residual disease absent	12(45%)	35(71%)

This shows how 55% of those with metastatic disease had residual disease, whereas only 29% of those with non metastatic disease had residual disease.

Age of children at presentation versus metastatic disease(n=76)

The age of children at the time of presentation(<=3 years or more than 3 years) was compared with the metastatic status of the disease. The results obtained are given below:

Table No.10: Metastatic versus localised disease in different age groups

	Metastases present	**No metastases**
Age <= 3 years	2(29%)	5(71%)
Age more than 3 years	25(36%)	44(64%)

Only 29 % of those aged less than 3 years at the time of diagnosis had metastatic disease, whereas 36 % of those older than 3 years at the time of diagnosis had metastatic disease. Student t-test was applied to the above data to look for correlation, however the p value was 0.24, indicating no statistical significance.

Duration of symptoms versus metastatic stage of disease (n=76)

The duration of symptoms prior to presentatione was analysed, in comparison with the metastatic state of the disease. The data obtained was as below:

Table No.11: Duration of symptoms versus stage of disease

	Metastatic disease	**Localised disease**
Duration<= 3 months	19(33%)	39(66%)
Duration > 3 months	8(45%)	10(55%)

It was seen that 33 % of those with duration of symptoms less than 3 months at the time of presentation had metastatic disease, whereas 45% of those with duration of symptoms more than 3 months at the time of presentation had metastatic disease. T- test was applied to the above data to look for significance, however the p value was 0.112, indicating no significance.

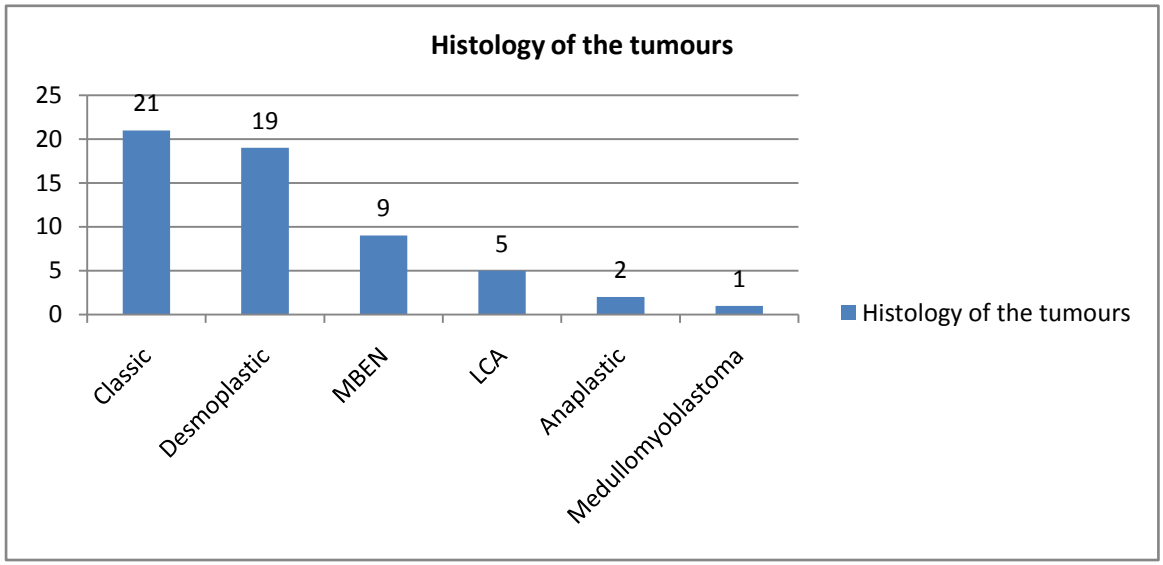
Histology of the tumours (n=57):

Of the 76 patients in the study group, detailed histology was available only in 57 cases. In the remaining 19 case the biopsy was reported as medulloblatoma WHO grade IV.

Table No.12: Histology of the tumours

Histology	Frequency
Classic	21(37%)
Desmoplastic	19(33%)
Medulloblastoma with extensive nodularity	9(16%)
Large cell anaplastic	5(9%)
Anaplastic	2(4%)
Medullomyoblastoma	1(2%)

Figure No. 7: Histology of the tumours



Majority of the tumours showed a classic histology, with desmoplastic forming the next most common category.

Histology and surgical excision:

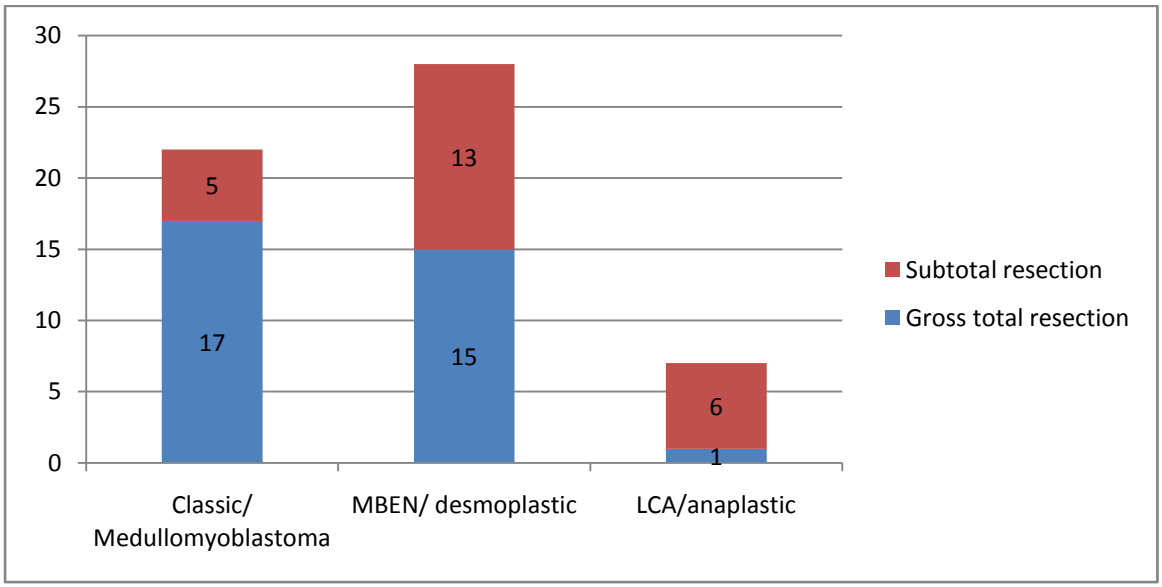
The completeness of resection was compared with the histology of the tumours. Since it has been shown that classic and medullomyoblastoma have similar outcomes, as do desmoplastic and MBEN(good outcome) and anaplstic and LCA(poor outcome), these were combined to form three groups- group 1 consisted of classic histology as well as medullomyoblastoma, group 2 consisted of desmoplastic medulloblastoma and medulloblastoma with extensive nodularity, and group 3 consisted of large cell anaplastic and anaplastic variant of medulloblastoma. It was found that majority of those belonging to classic/ medullomyoblastoma group (17 out of 22, 7%), had gross total resection of the tumour. In the group comprised of desmoplastic medulloblastoma and medulloblastoma with extensive nodularity, 15 out of 28(54%) had undergone gross total resection. In the last group of large cell anaplastic and anaplastic variants, only 1 out of 7(14%) could be resected completely. T-test was applied to this data to look for significance, however, the p value was 0.47, which was not significant. The results obtained when comparing the frequency of gross total resection and subtotal resection of tumours in relation to these groups, is depicted below.

Table No.13: Frequency of gross total and subtotal surgical resections among the different histological variants

Histology	**Gross total resection**	**Subtotal resection**	**Total frequency**
Classic +medullomyoblastoma	17	5	22
Desmoplastic/ MBEN	15	13	28

Large cell anaplastic/ anaplastic	1	6	7
Total	33	24	57

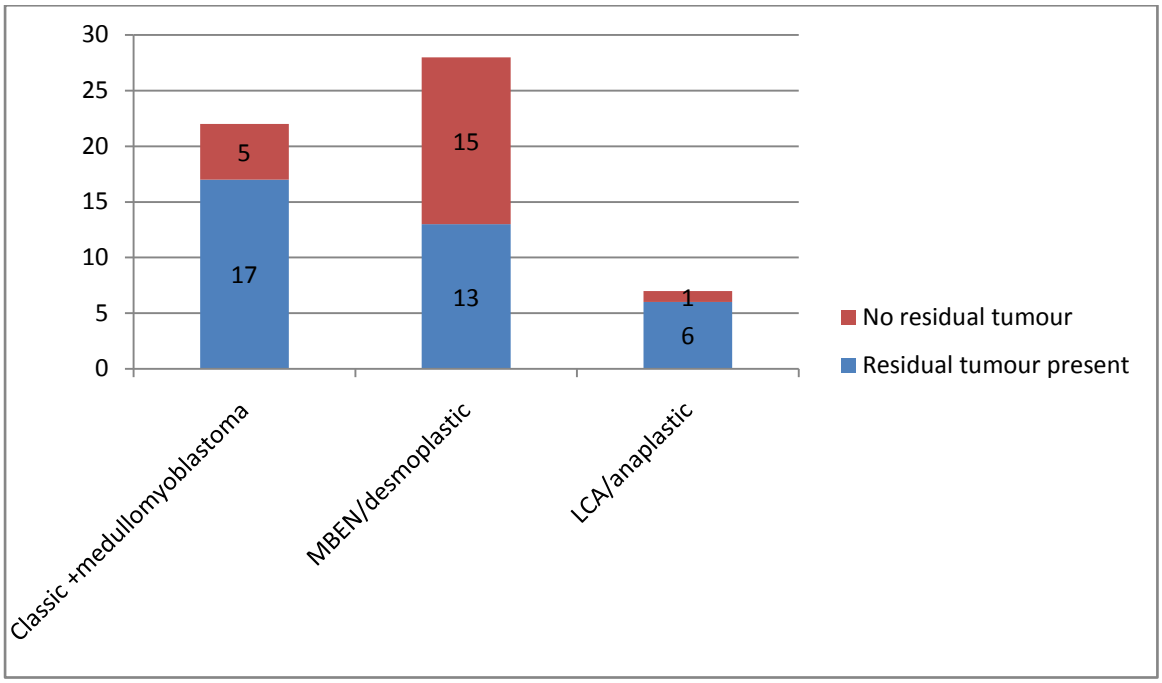
Figure No. 8: Histological variants and completeness of surgical resection:



Histology in comparison with presence of residual tumour:

The histology of the tumour was compared with presence of residual tumour in the post-operative scans. 17 out of the 22(77%) tumours exhibiting classic/medullomyoblastoma histology showed residual tumours in the post-operative scans. 13 out of 15 tumours (86%) of the tumours in the desmoplastic/ MBEN group and 6 out of the 7 (86%) tumours in the LCA/ anaplastic group showed evidence of residual tumours on the post-operative scans. T- test was applied to this data, to look for significance, the result of which was 0.6081, which was not significant. The results of the same are depicted below:

Figure No. 9: Histological types and presence of residual tumour



Risk stratification

Risk stratification was done based on (i) age at presentation (ii) extent of surgery (iii) metastatic vs localised disease based on CSF & MRI spine

Histology and stage of disease

The histological types and the presence of metastases were assessed by comparing histology with CSF cytospin results and MRI spine results.

Table No. 14: CSF cytospin results and comparison with histology

Histology	CSF cytospin positive	CSF cytospin negative	CSF cytospin unsatisfactory	Cytospin not done
Classic + medullomyoblastoma(n=22)	**1(5%)**	**8(36%)**	**4(18%)**	**9(41%)**
Desmoplastic +MBEN(n=28)	**2(7%)**	**12(43%)**	**3(11%)**	**11(39%)**
Anaplastic +LCA(n=7)	**2**	**2**	**0**	**3**

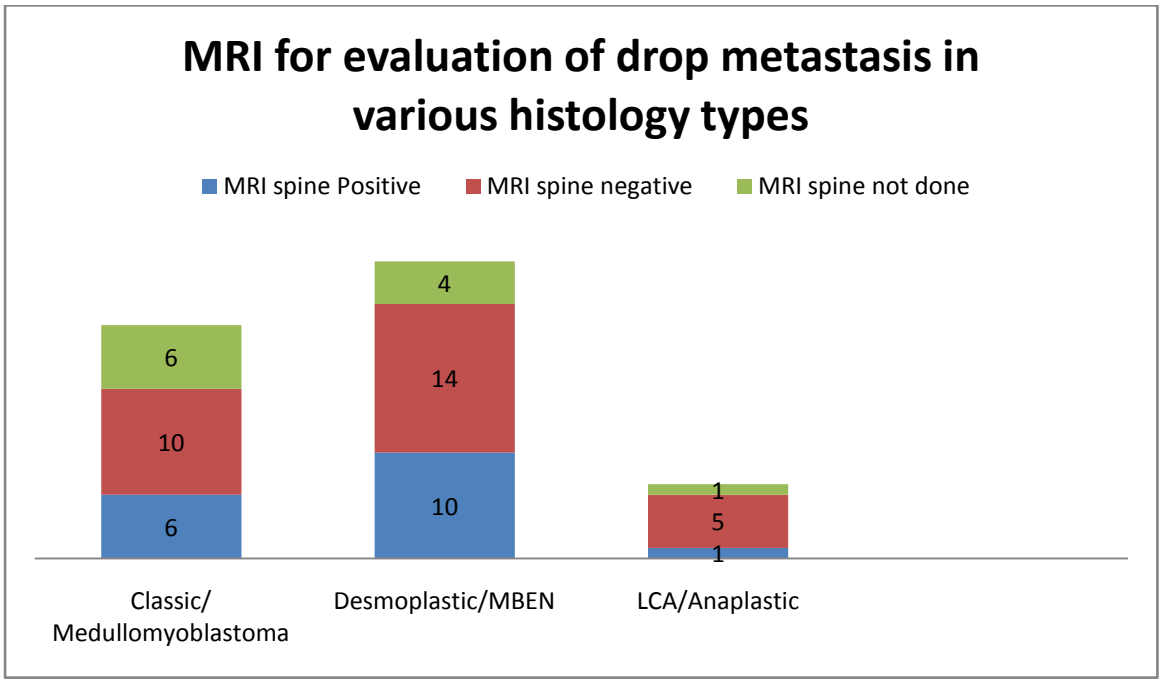
Only one of the 22(5%) in the classic histology group had evidence of metastases whereas 2 of 28(7%) and 2 out of 7(29%) of those in desmoplastic and anaplastic group had evidence of metastatic disease.

Table No.15: MRI spine screening results with histology:

Histology	MRI spine s/o metastases	MRI spine negative for metastases	MRI spine not done
Classic + medullomyoblastoma	6(27%)	10(46%)	6(27%)
Desmoplastic + MBEN	10(36%)	14(50%)	4(14%)
Anaplastic + LCA	1(14%)	5(72%)	1(14%)

39 out of the total 76(51%) had undergone both MRI spine screening as well as CSF cytology as part of metastatic workup. Both were positive in 6 , both were negative in 20, whereas MRI spine was positive in 11 with negative cytology, and CSF was positive in one with negative MRI.

Figure No.10: MRI spine for evaluation of drop metastasis among various histological types.



Risk stratification of the tumours (n=76):

Based on the risk stratification methods proposed by Packer et al, the entire population was divided into standard risk and high risk groups. Those whose age at diagnosis was less than 3 years, had metastases at the time of diagnoses or had residual tumour volume of >1.5 cm2 were treated as high risk disease, whereas those whose age was more than 3 years at the time of diagnosis, had non-metastatic disease at the time of presentation and had residual tumour volume of <1.5 cm2 at the end of surgery were classified as standard risk disease.

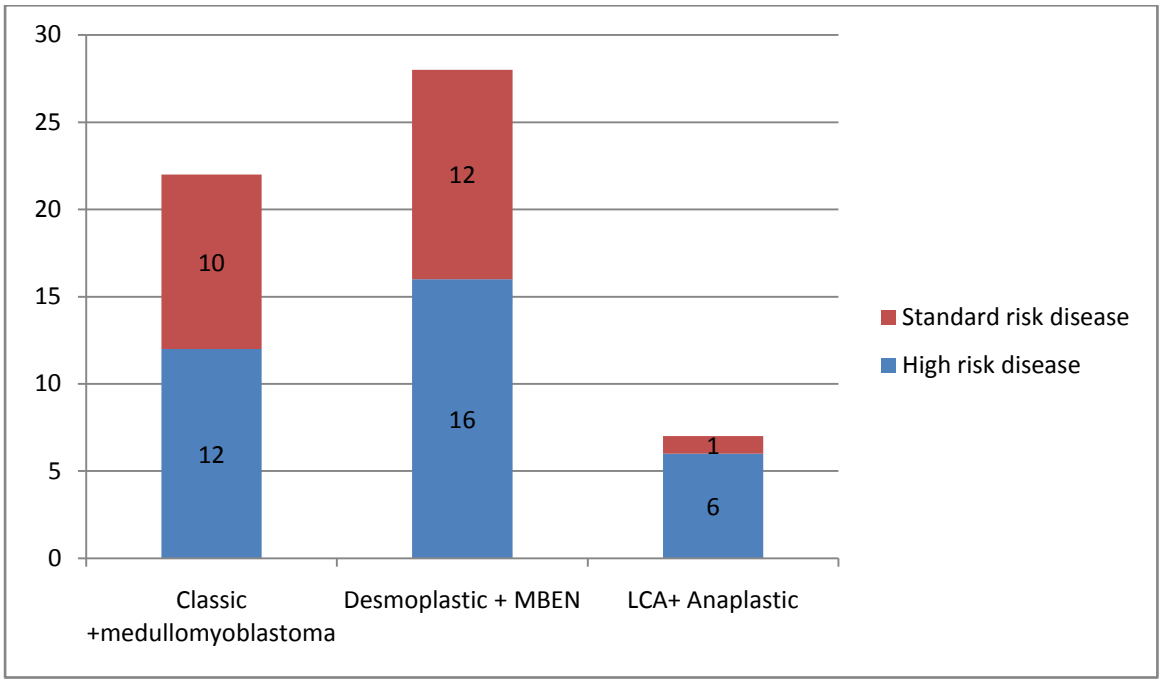
Table No.16: Risk stratification of the tumours

Factor for stratification	Standard risk	High risk
Age at presentation(<=3 yrs vs >3 yrs) (n=76)	69	7
Metastatic disease (present or not) (n=76)	49	27
Residual disease(present or not) N(n=76)	46	30

According to this, 43 patients (57%) fell in the high risk category whereas the remaining 33(43%) were in the standard risk category.

According to the histological groups, 12 of the 22(55%) of the classic/ medullomyoblastoma group were high risk disease. 16 of the 28(57%) in the desmoplastic/ MBEN group were high risk and 6 out of 7(86%) in the anaplastic/LCA group were from the high risk disease category.

Figure No. 11: Risk stratification among the histological types.



Post operative treatment (Radiotherapy and chemotherapy)

Radiotherapy(n=57)

Of the 76 patients who had reported to the paediatric haematology-oncology unit after surgery, 71 reported to the radiotherapy department for treatment. Out of these, 7 were not eligible for radiotherapy as they were less than 3 years of age at the time of diagnosis. Of the remaining 64, 57(89%) completed their radiotherapy here. 2 completed radiotherapy elsewhere before coming for further chemotherapy here at a later date. Hence, of the 76 who had presented, only ten had defaulted therapy before commencement of radiotherapy.

Time interval between surgery and radiotherapy (n=59):

According to the COG (Children's Oncology Group) guidelines, the optimum gap between surgical excision and radiotherapy is 2 weeks- 4 weeks, i.e, radiotherapy can commence once 2 weeks of post-operative period is over and should ideally commence before 4 weeks

are over. The SIOP guidelines also recommend commencement of radiotherapy within 4-6 weeks. The mean gap between surgery and commencement of radiotherapy among the 59 children who took radiotherapy either in this institute or elsewhere was looked at, and was found to be 33.36 days+/-18. The least gap was 11 days, and the maximum gap was 96 days. In the study population, 4(7%) commenced RT before 14 post-operative days were completed, 42(71%) commenced RT between 15-42 days post-operatively, whereas 13 (22%) commenced RT after more than 43 days post-operatively. These delays occurred as a result of post-operative complications such as meningitis (8 of the 13 cases with delay in commencement of RT), CSF leak (3 out of 13) and stormy post-operative course with haematoma in tumour beds (2 out of 13), etc. The timing of commencement of radiotherapy was appropriate in 71 % of the total study population.

Figure No.12: Timing of commencement of radiotherapy:

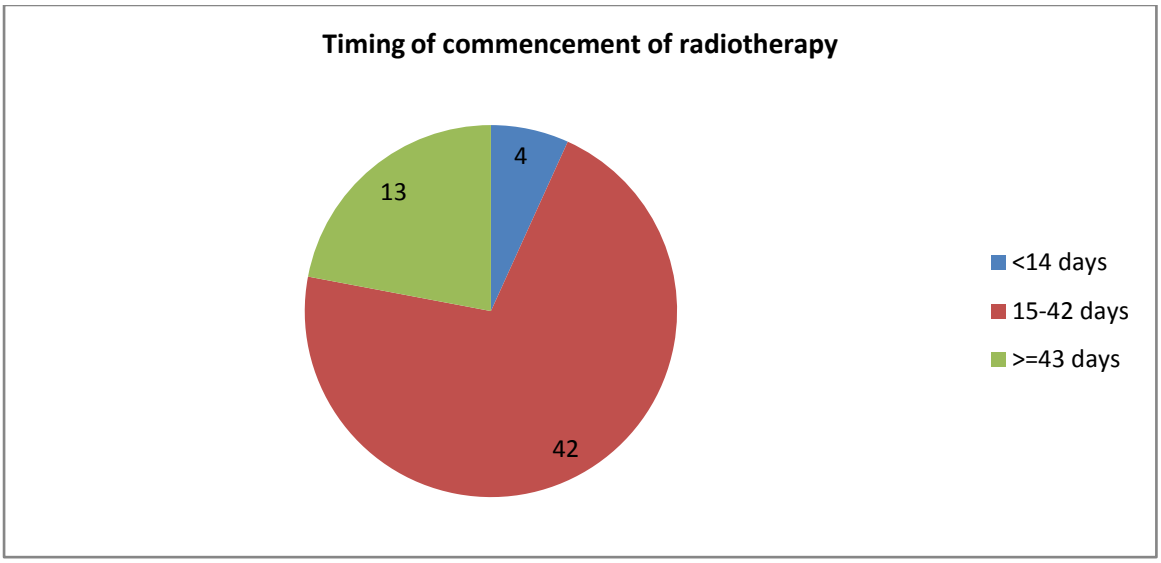
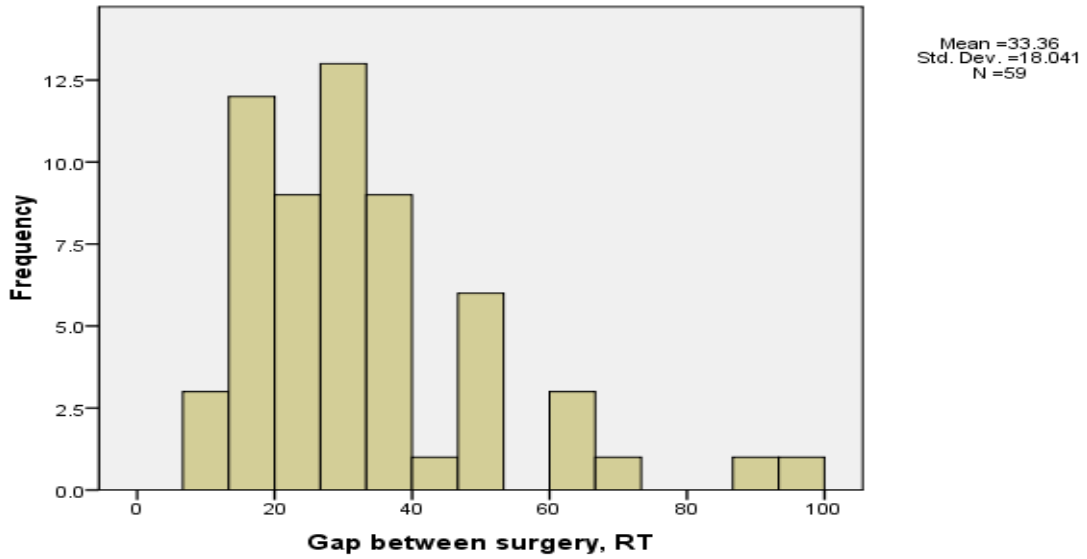


Figure No.13: Time interval between surgery and radiotherapy:



Complications of radiotherapy (n=57):

Of those who underwent radiotherapy here, 50% had radiotherapy induced complications. These complications were significant enough to cause a delay in completion of radiotherapy among 21(37 %). The mean delay was 13 days, and the longest, 25 days. The various complications encountered by those who underwent radiotherapy are listed below:

Table No:17- Complications of radiotherapy:

Complication	**Frequency**
Neutropenia	18(32%)
Radiation induced skin reactions	8(14%)
Hypertension	2(4%)
Mucositis	2(4%)
Herpes zoster reactivation	2(4%)
Optic atrophy	1(2%)
Stent infection	1(2%)

Steroid induced gastritis	1(2%)
Pancreatitis	2(4%)
Seizure	1(2%)
Vertigo	1(2%)

The dose of radiotherapy given was looked at. The standard recommendation according to the SIOP guidelines were 36 Gy of radiation to the craniospinal region with a posterior fossa boost of 18 Gy. 44 of the 59(75%) were able to complete 36 Gy of RT to the craniospinal region with a posterior fossa boost of 18 Gy. 3 patients (5%) with high risk disease received additional RT when compared to the rest. 4 patients (7%) got less than 18 Gy boost to the posterior fossa as their radiotherapy schedule had been prolonged by more than 2 weeks.

Chemotherapy (n=60):

Of the 76 patients who had presented to paediatric haemato-oncology department, 60 (79%) took chemotherapy at this centre.

Time interval between RT and chemotherapy (n=60):

The Packer regimen for chemotherapy advocated 6 weeks as the ideal interval between completion of radiotherapy and commencement of chemotherapy. Our institute follows the Packer regimen for children more than 3 years of age at the time of diagnosis, with 8 cycles of chemotherapy with lomustin, cisplatin and weekly vincristine starting 6 weeks from the time of completion of radiotherapy. 56 patients were treated with Packer regimen. 4 of this 56 (7%) had commenced chemotherapy before 42 days, 31(54%) commenced chemotherapy within an interval of 43-56 days and 21(38%) started their chemotherapy only after more than 57 days after completion of chemotherapy. The reasons for delay in

chemotherapy was patients presenting late (16 cases), prolonged neutropenia after radiotherapy (2), recurrent pancreatitis (1) and meningitis (1)., 1 had meningitis and 1 had completed radiotherapy elsewhere before presenting here with extraneural metastases for treatment. Timing of commencement of chemotherapy was appropriate in 54 % of the 56 patients treated with the Packer regimen. The mean interval between RT and chemotherapy was looked at, and was found to be 56.08 days +/-19.19. The minimum interval between RT and chemotherapy was 21 days. There was a single patient who commenced his chemotherapy 600 days after his radiotherapy was completed. This patient had undergone his surgery and radiotherapy elsewhere, and had presented 1 year and 9 months after completion of radiotherapy with extraneural metastases.

4 of these 60 had been treated with baby brain protocol as they were less than 3 years of age at the time of diagnosis. The baby brain protocol states that idea time of commencement of post-operative chemotherapy was between 2-3 weeks after surgical resection. Among the 4 children who were treated with baby brain protocol, chemotherapy was started within 21 days for 3 children, whereas one child started after 64 days as he had completed his surgical excision elsewhere and presented here after 2 months for further management. Hence timing of commencement of chemotherapy was appropriate in 75% of these patients (3 out of 4 patients). Mean interval between surgery and chemotherapy was 25.4 days +/-20.

Figure No. 14: Interval between radiotherapy completion and commencement of chemotherapy:

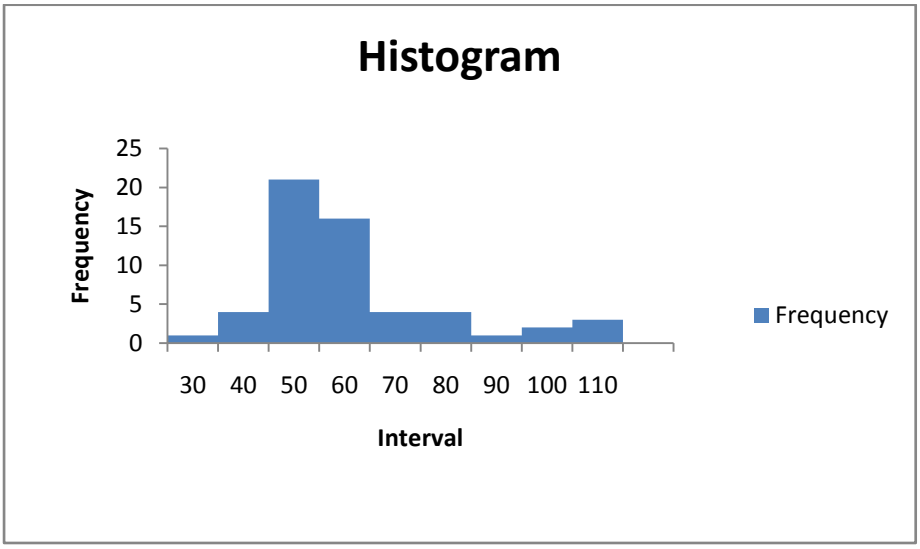
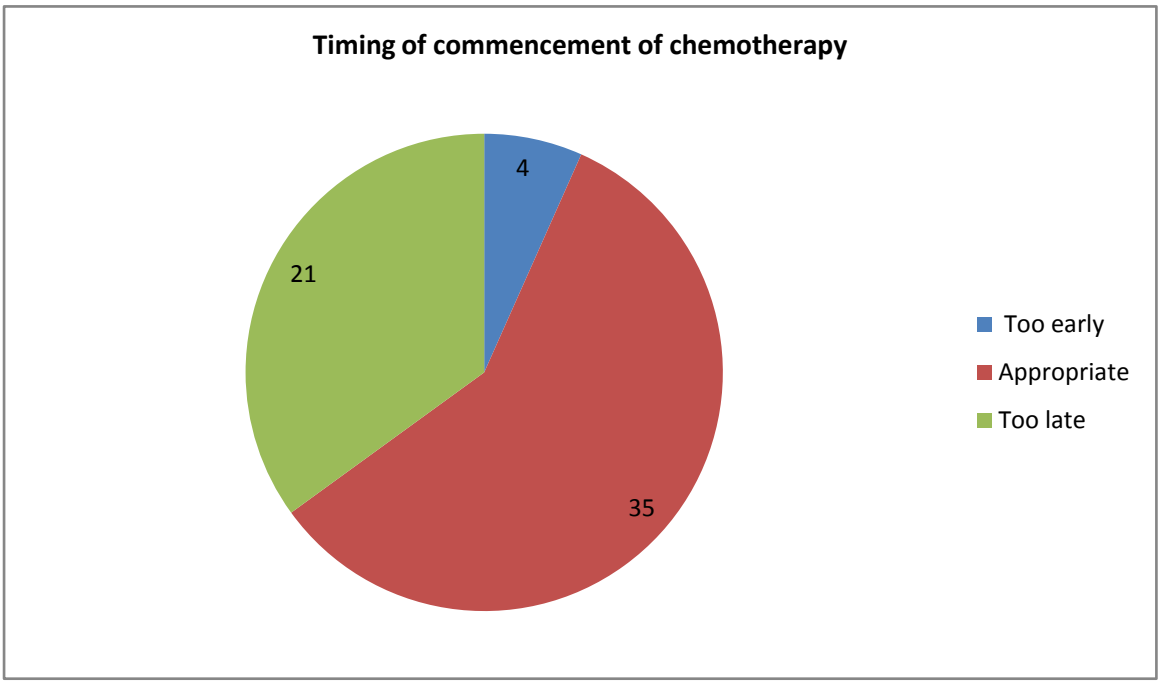


Figure No. 15: Timing of commencement of chemotherapy



Details of chemotherapy (n=60):

All patients who were more than 3 years at the time of diagnosis were planned for chemotherapy based on Packer regimen, with 8 cycles of chemotherapy being planned. The mean number of chemotherapy cycles received by each patient was 6.63, with a standard deviation of 2.2. The median number of cycles of chemotherapy received was 8. The least number of cycles received was 1, where the patient discontinued chemotherapy after the first cycle and was thereafter lost to follow up. The maximum cycles of chemotherapy received were 8 cycles. The ones who were treated with baby brain protocols were planned for 7 cycles according to SFOP regimen.

The number of chemotherapy cycles received by the children treated under this institute are depicted below:

Table No. 18: Number of chemotherapy cycles taken:

Number of cycles of chemotherapy taken here	**Frequency**	**Percentage**
8	36	60
7	5	8
6	6	10
5	2	3
4	3	5
3	0	0
2	3	5
1	5	8

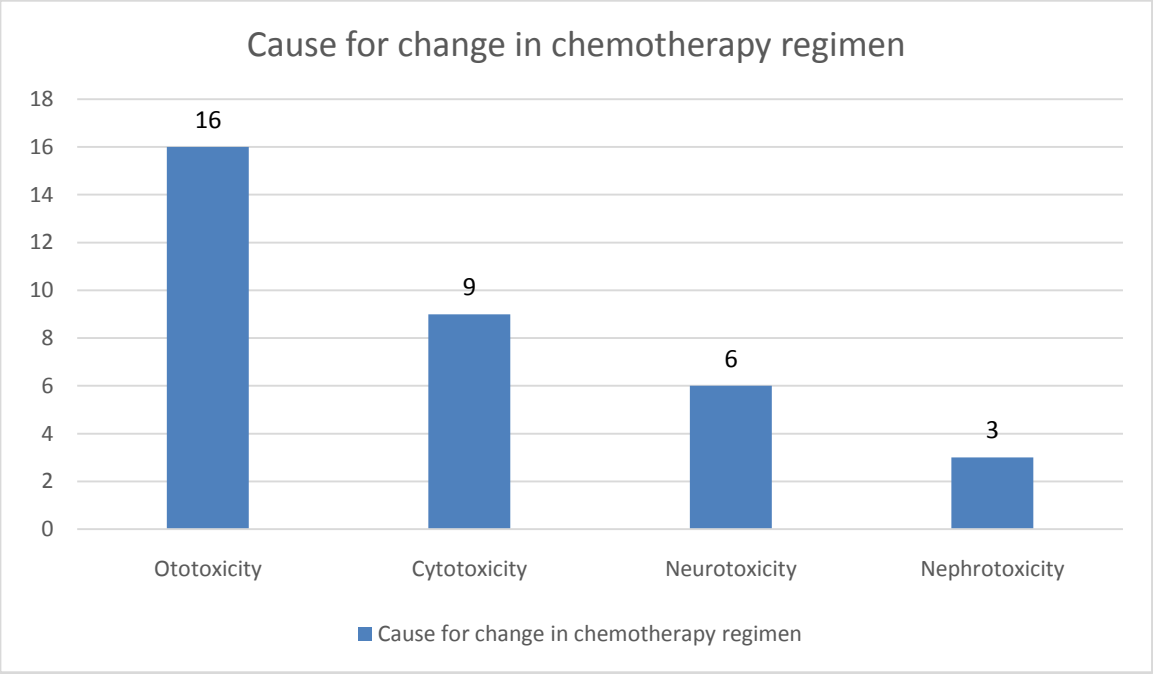
Of the 56 patients treated with Packer regimen chemotherapy, 36 had completed all 8 cycles of chemotherapy. Of the remaining 20, treatment was stopped prematurely for 9 due to toxicities- profound hearing loss, neurotoxicity or prolonged cytopenia. 2 children died while on chemotherapy, one due to septic shock and one due to unknown causes (she was brought gasping to casualty after PCV cycle 6, and could not be resuscitated). 47 out of the 60(78%) had completed their chemotherapy and 11 out of 60(18%) had defaulted treatment, whereas two (3%) had died while on chemotherapy.

Of the four who were on baby brain protocol, 2 had completed 7 cycles of chemotherapy with carboplatin, procarbazine, cisplatin, etoposide, cyclophosphamide and vincristine as per protocol, however 2 of them had only 6 and 2 cycles respectively before having disease progression and discontinuing treatment.

Treatment modifications (n=60)

24 of the 60 who had chemotherapy had changes in their drug regimen. This change was due to the following reasons- ototoxicity as a result of cisplatin, cytotoxicity as a result of lomustin and vincristine, neuropathy as a result of vincristine or nephrotoxicity due to cisplatin. If cytopenia was significant, lomustin was omitted, and carboplatin was substituted for those with significant hearing loss/ renal tubular issues. Vincristine dose was decreased for cytopenia and omitted if neuropathy was significant. The reason for modifications in treatment regimen is documented below:

Figure No. 16: Reasons for change in chemotherapy regimen



The mean duration of cytopenia associated with chemotherapy was 9.28+/-19.37 after PCV(week 1). 4 patients had their chemotherapy protocol truncated as a result of prolonged cytopenia, whereas a total of 9 patients had changes in their protocol as a result of cytopenia. The changes in the protocol were as mentioned above.Musial Bright et al in their studies on susbstitution of carboplatin for cisplatin in order to decrease the ototoxicity of the regimen found that the efficacy of the drug was as good as that of cisplatin with significant reduction in the hearing loss involved.(85)

Outcome

The table given below depicts the treatment received by the children.

Table No.19: Treatment received by the cohort:

Category	Frequency	Percentage
Total number in the study	76	100
Surgery alone	16	21
Surgery + Radiotherapy	0	-
Surgery + Radiotherapy +Chemotherapy	60*	79

*4 children were too young to receive RT

The above table represents the treatment received by the children

Table No. 20: Outcome of children at the time of analysis of this study.

Treatment outcome	Frequency	Percentage
Completed treatment, in complete remission	32	42
Completed treatment Relapsed, on palliative treatment	2	3
Completed treatment, lost to follow up	4	5
Died (disease/other complications)	19	25

Abandoned treatment	5	7
Refused treatment	14	18

We have defined lost to follow up as patients who completed treatment, achieved disease remission and subsequently who failed to review for more than 36 months and were not contactable. Those who had started treatment at this institute, but defaulted treatment prior to completion of all the planned treatment as per protocol, irrespective of complications, were considered to have abandoned treatment.

In our patient population, we had 4 who were lost to follow up. Among the 32 with disease remission and on follow up, 17 have been in disease remission for 2 years or less, whereas 8 have been in CR for between 2 to 5 years and 7 have been in disease remission for more than 5 years, and can therefore be considered to have survived this disease.

Figure No. 17:- Follow up details:

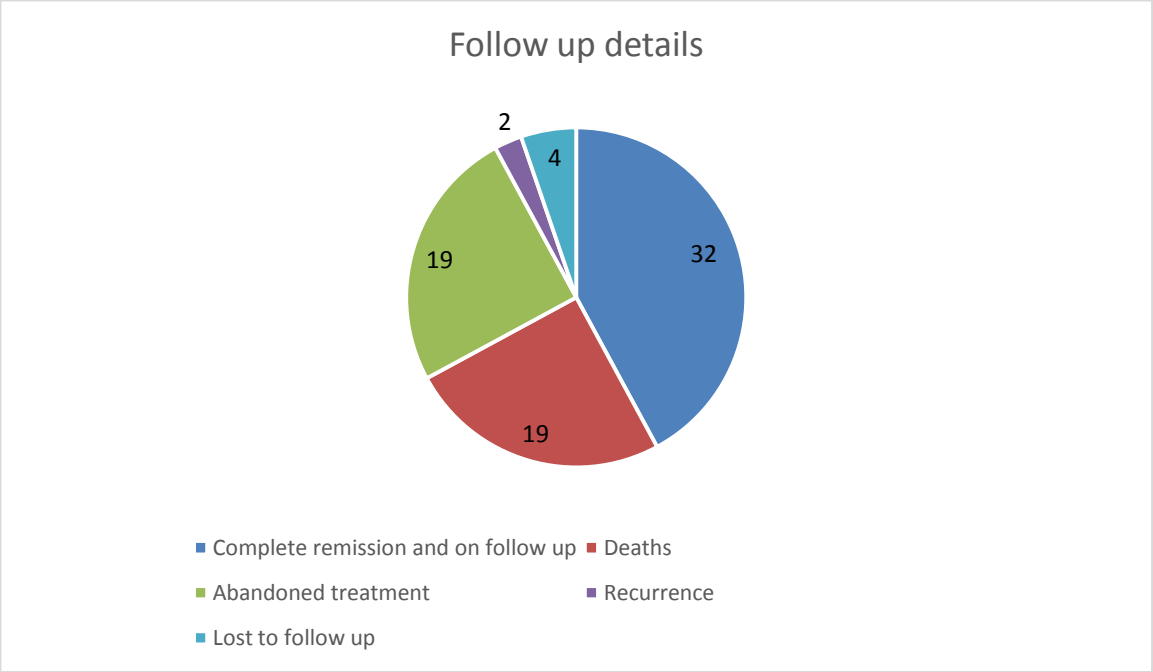
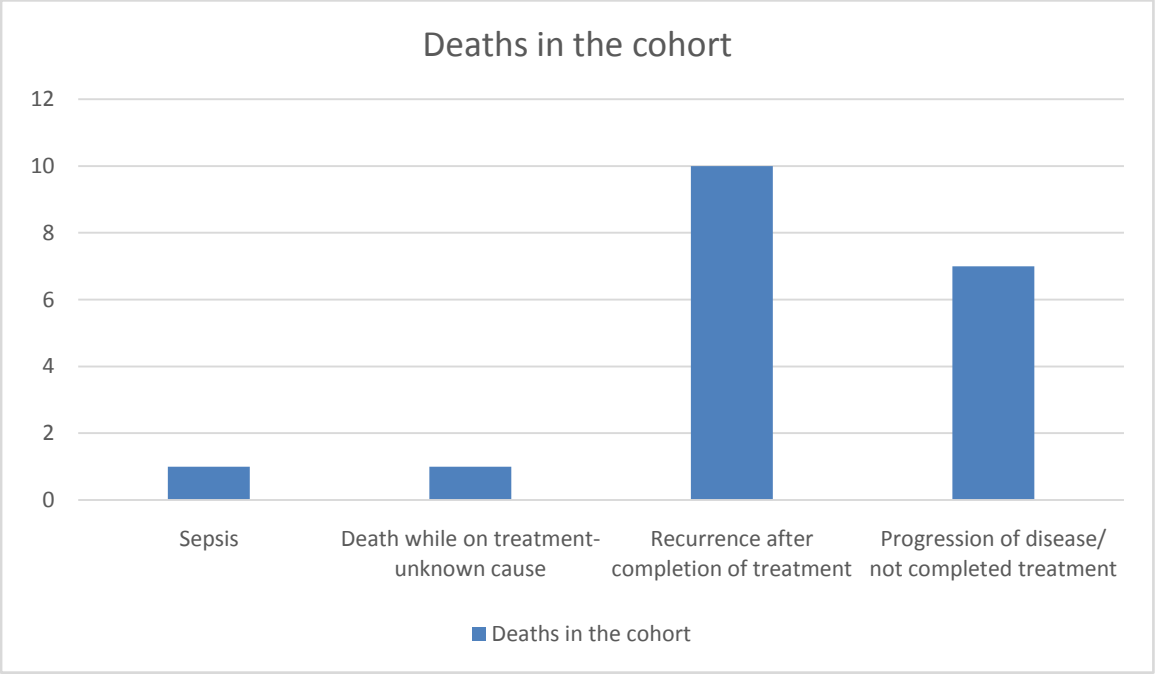


Figure No.18: Cause of death



Data of 19 children who died were available for analysis. 14/19 (74%) had high risk disease. The mortality rate among those with standard risk disease was 15% (5/33) and those with high risk disease it was 33 %(14/43).

Table No. 21: Treatment outcomes in comparison with different risk factors (n=76)

	Complete remission	Recurrence	Death	Treatment abandoned
<= 3 years	4(57%)	0	2(29%)	1(14%)
>3 years	32(46%)	2(3%)	17(25%)	17(25%)
Gross total resection	27(68%)	0	8(17%)	13(27%)

Subtotal resection	9(32%)	2(7%)	12(43%)	5(18%)
Metastases present	12(37%)	2(7%)	9(33%)	4(15%)
Metastases absent	24(49%)	0(0%)	11(22%)	14(29%)

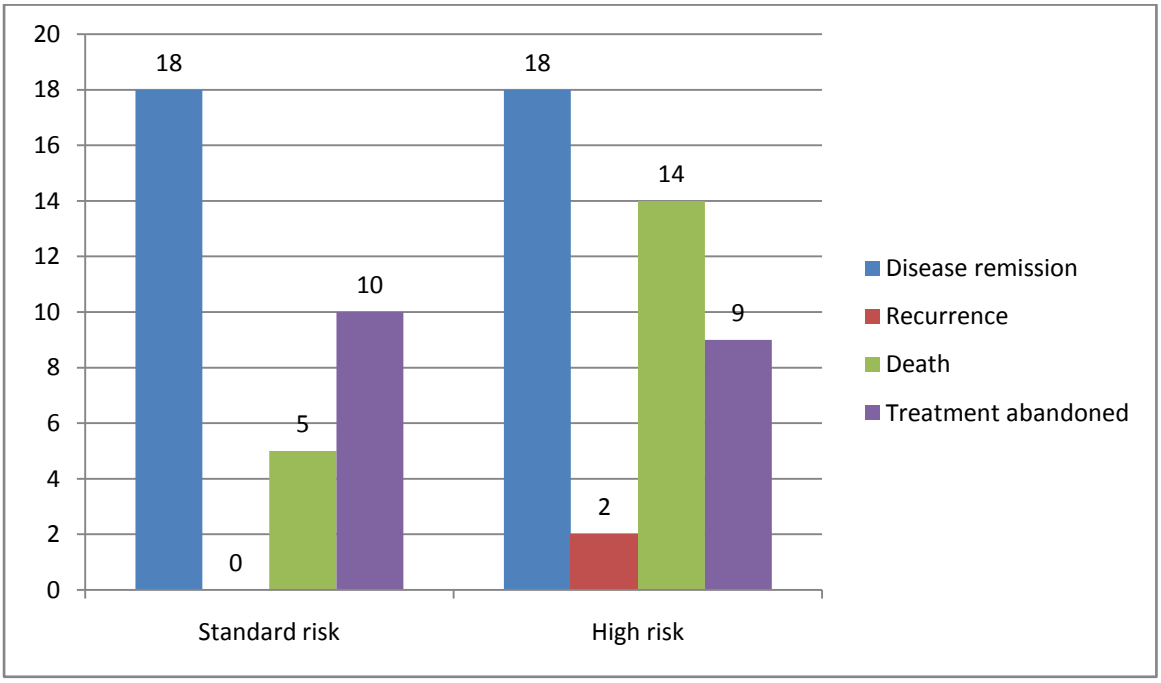
High risk disease versus standard risk disease:

Using age less than or equal to 3 years, gross residual tumour and metastatic disease as indicators of high risk disease as proposed by Packer, we found that our study population had 33 patients in the standard risk category and 43 in the high risk category by at least one of the above criteria. The outcomes among these two groups were as follows:

Table No. 22: Outcome among standard risk group compared with that of high risk group

Outcome	Disease remission	Recurrence	Death	Treatment abandoned
Standard risk **(n=33)**	18	0	5	10
High risk **(n=43)**	18	2	14	9

Figure No. 19: Comparison of outcome among high risk group versus standard risk group



Comparison of outcome of the various histological types (n=52):

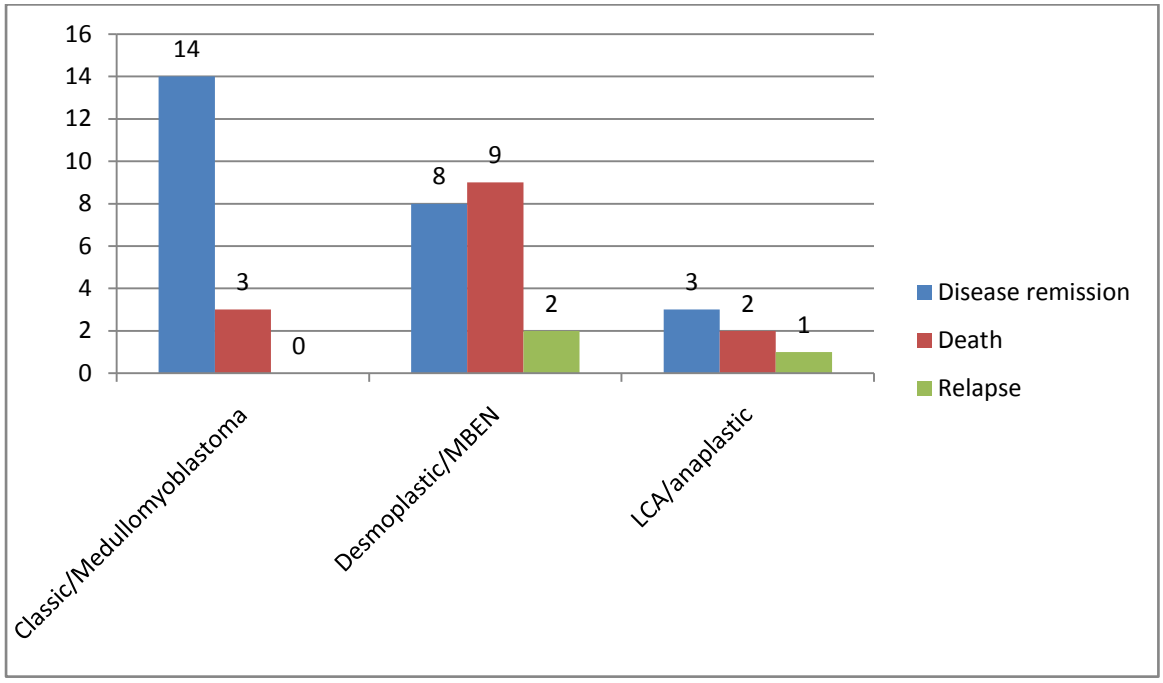
The outcome of the various histological types were combined into similar histological types and analysed, among the ones whose outcome was known. There were no statistically significant difference between the different types.

Table No. 23: Outcome of various histological subtypes

Histological subtypes	Total number	Disease remission	Death	Relapse, on palliative chemo
Classic+ Medullomyoblastoma	17	14	3	0
Desmoplastic +MBEN	19	8	9	2

Anaplastic + LCA	6	3	2	1

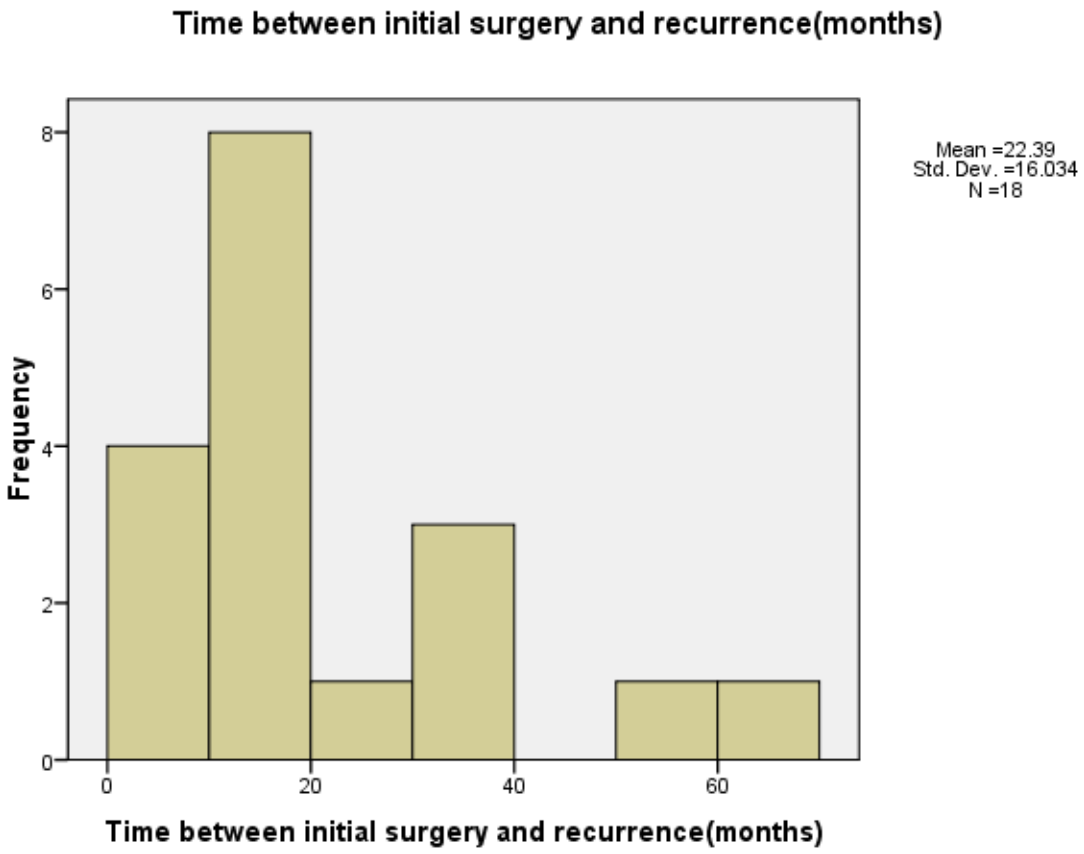
Figure No. 20: Outcome of various histological types:



<u>Outcome of those who had recurrence of tumour (n=19):</u>

Of the 19 who had disease recurrence, only two are still alive, on palliative chemotherapy whereas the rest had expired. The mean duration between surgery and recurrence was considered, since a few hadn't completed their treatment (radiotherapy and chemotherapy). The mean duration in months between primary surgery and recurrence was 22.39, with a standard deviation of 16.03. The median interval was 17.5 months. The minimum interval was 4 months, and the maximum duration was 67 months after surgery.

Figure No. 21: Time interval between initial surgery and recurrence:



Of the 19 with disease recurrence, 16 (84%) were high risk and 3(16%) were low risk according to the risk stratification methods described by Packer et al. Gross total resection of the tumour had been done with a residual tumour volume less than 1.5 cm2 on post-operative imaging, in 6 of the 19(32%), whereas 13 out of 19 (68%) had undergone subtotal resection, with a residual tumour volume of more than 1.5 cm2. Metastatic disease was present in 10 out of 19(53%). The age at diagnosis was less than 3 years in 2 of the 19 children (12%).

Comparison of different age groups at diagnosis with the prognosis (n=76):

There were 7 children who were aged 3 years or less at the time of diagnosis. Of these, only 6 commenced chemotherapy. 4 did well, and are in clinical remission with disease-free intervals of 8 years, 5 years, 4 years and 3 years respectively. One was lost to follow up before commencing chemotherapy. The other two, who started chemotherapy, had progression of disease while on chemotherapy, and discontinued treatment. Subsequently, it has been informed that these two expired of disease.

69 of the 76 patients (91%) were aged more than 3 years at the time of presentation. Of these, 32 had disease remission (46%), 2(3%) have disease recurrence and are currently on palliative chemotherapy, 18(26 %) have been lost to follow up and 17(25%) have expired.

Table No. 24: The outcome for those less than 3 years compared with those older than 3 years at the time of diagnosis

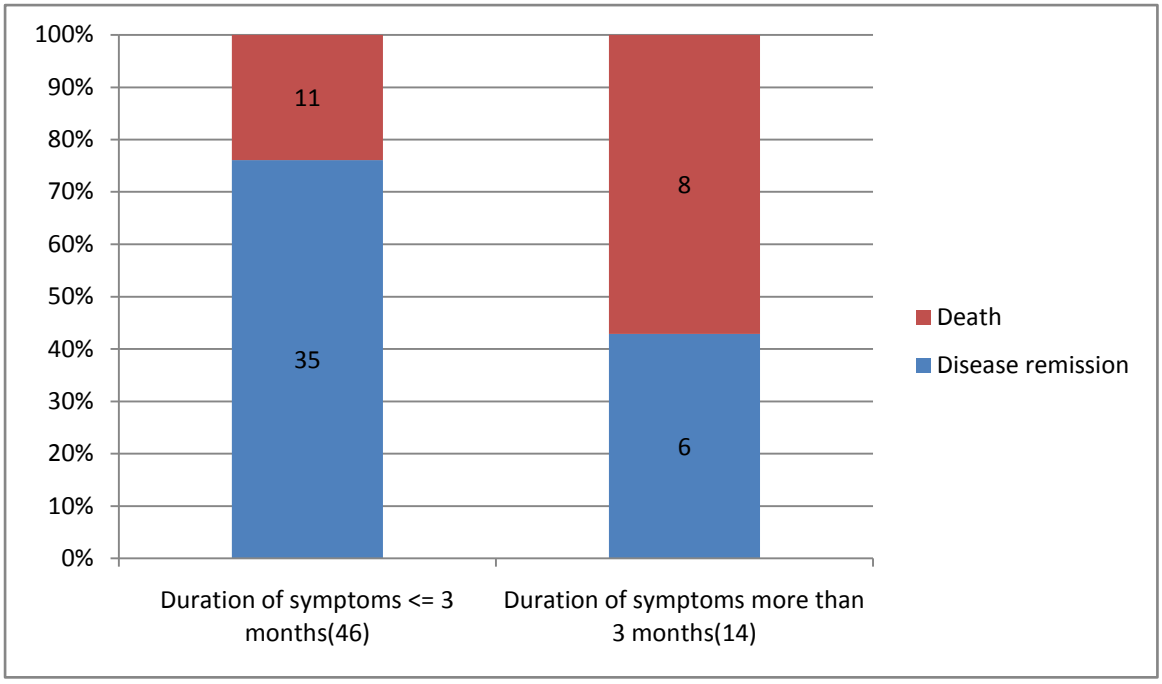
Age at diagnosis(in years)	Disease remission	Recurrence	Death	Treatment abandoned
<=3(n=7)	4	0	2	1
>3(n=69)	32	2	17	18

Since age less than 3 years was considered to be high risk according to the risk stratification proposed by Packer et al, the outcome of those who were less than 3 years of age at the time of diagnosis was compared with those who were older than 3 years at the time of diagnosis of medulloblastoma. The data given above was analysed using Pearson chi-square test. The p value for this data was 0.98, which shows that there was no statistically significant difference between the two groups.

Duration of symptoms at the time of presentation vs outcome

The final outcome was also compared among those with varying duration of symptoms at the time of presentation, namely more than 3 months and less than 3 months at the time of diagnosis. Among the 46 people who had presented before 3 months of symptoms, 35 are in disease remission and 11 had died. Among 14 patients who presented only after more than 3 months of symptoms, 6 were cured and 8 had died. Fisher's exact test was used for analysis of the above data, and a p value of 0.054 was obtained, which showed that there was no statistically significant difference between the two groups in terms of outcome.

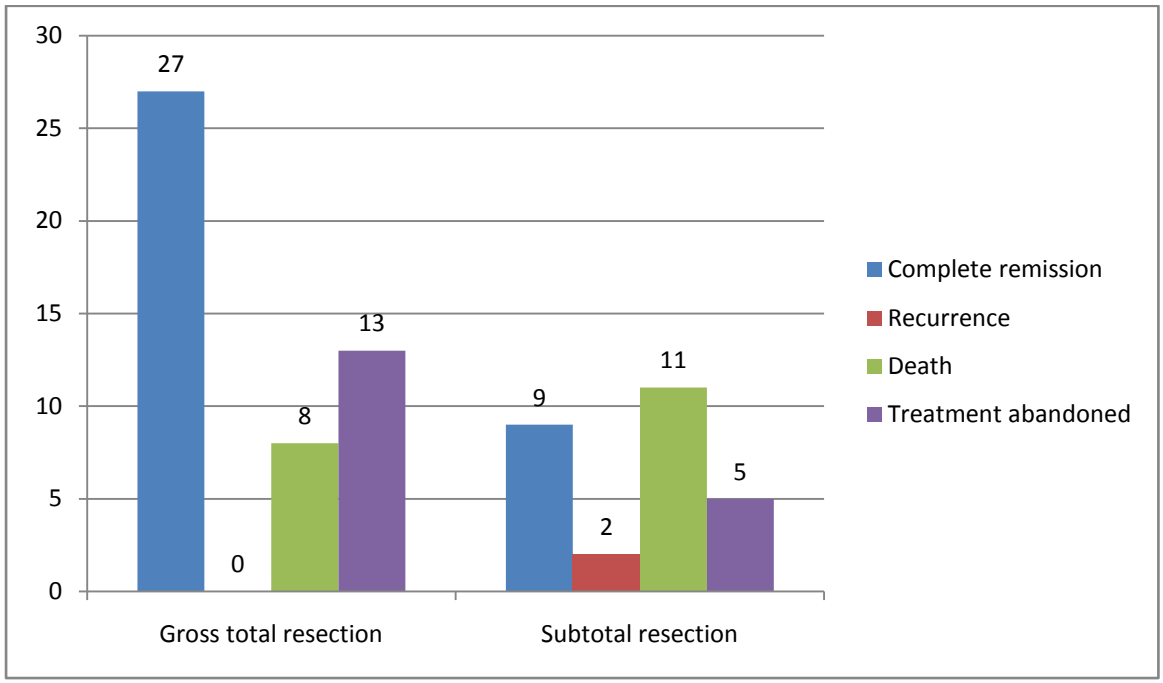
Figure No. 22: Comparison of outcome of those with varying duration of symptoms at the time of diagnosis



Comparison between the outcome of those who had gross total excision of the tumour with those who had subtotal excision of tumour:

The outcome of those who had subtotal excision of tumour was compared with those who underwent gross resection of the tumour. Among those with gross total resection, 27 were in complete remission, 8 had died and 13 had abandoned treatment. Among those who had undergone subtotal resection, 9 had achieved complete remission, 2 had had recurrence, 12 had died and 5 had abandoned treatment. Pearson's chi square was applied to this data to look for correlation, however the p value obtained was 0.238, hence this was not significant.

Figure No. 23: Comparison of outcome among those with subtotal resection of the tumour vs those with gross total resection of the tumour:



Late effects of treatment in children with medulloblastoma

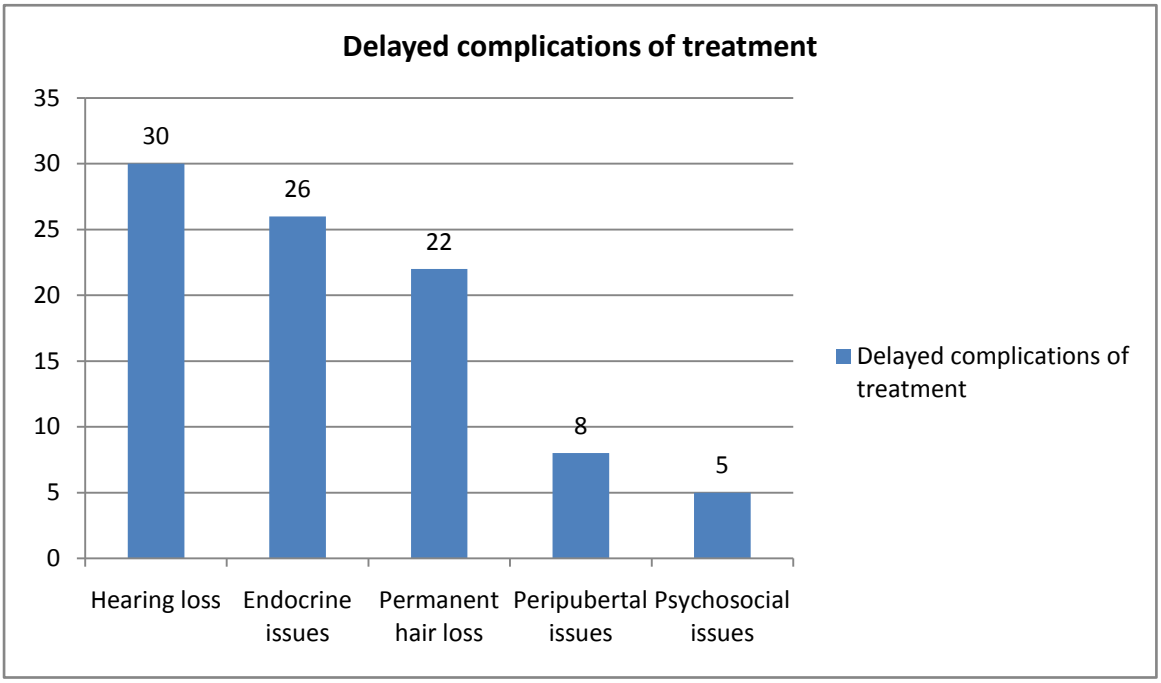
48 children were followed up for delayed complications of treatment in this group**.** This assessment was done at the time of completion of treatment, however was updated at each review. The common complications seen were peripubertal issues, hearing loss, permanent hair loss, endocrine issues and psychosocial issues. Delayed puberty was seen in 6, with premature ovarian failure in 2. Hearing loss, significant enough to affect daily life, i.e, moderate to profound hearing loss, was seen in 12 patients, whereas 30 of the 47 had some degree of hearing loss. Permanent hair loss was seen in 22 children who had completed treatment. The various endocrine issues have described in detail below. Depression, excessive aggression, attention-deficit hyperactivity syndrome and other behavioural issues were seen in a few children, for which they have been assessed by child psychiatrists and developmental paediatricians, and are on follow up for the same. None of the children had expressed suicidal ideation in the follow up cohort.

Table No.25: Late effects of treatment

Complication	**Frequency**	**Percentage**
Hearing loss	30	62%
Endocrine issues	26	55%
Permanent hair loss	22	46%
Peripubertal issues	8	17%

The frequency of the delayed effects of treatment are shown below:

Figure No. 24: Delayed complications of treatment:



Of the 30 who had hearing loss, 12 have moderate to severe sensorineural hearing loss, and have been advised hearing aids for the same.

Endocrine dysfunction(n=48)

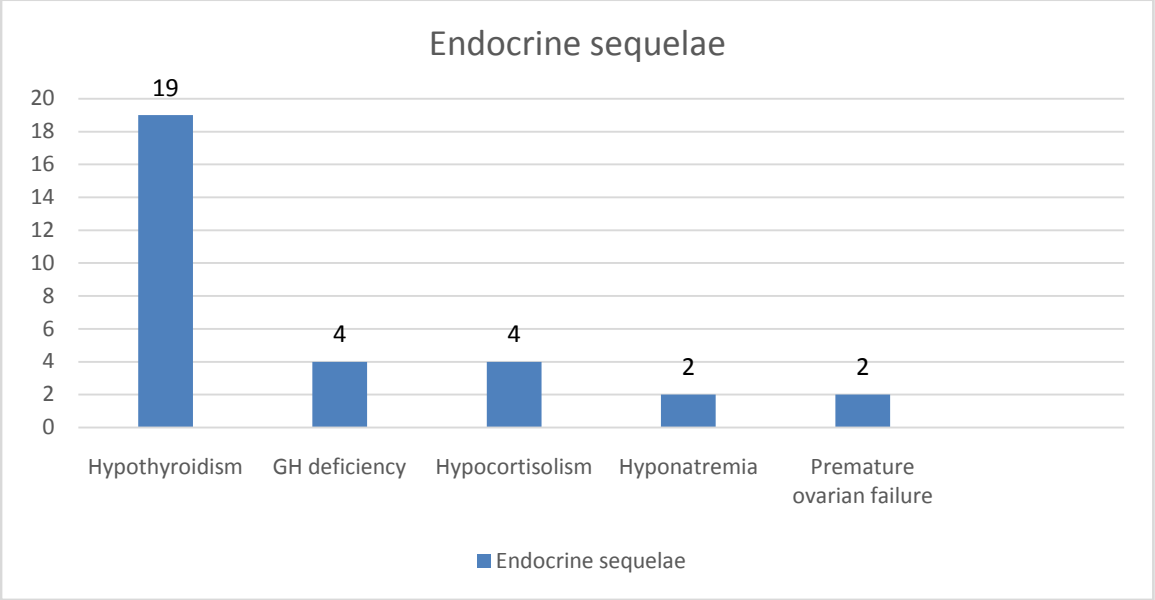
It is well known that the survivors of medulloblastoma have varying degrees of endocrine dysfunction as a result of radiation exposure to the head and neck region. These late-effects are some of the most frequently studied late effects seen in survivors of childhood malignancies, especially central nervous system malignancies.

We looked at the various endocrine issues among our study population and found that 26 of the 48 had endocrine sequelae. Hypothyroidism was seen in 19 children, who are on regular thyroxine supplementation. Compliance has been good in most cases, and the parents recognise the need for therapy. Hypocortisolism was seen in 2 children, who are on hydrocortisone supplements for the same. Though short stature was seen in many of the

survivors, only 4 were identified to have GH deficiency. Premature ovarian failure was seen in 2 of the survivors, and 6 children had had delayed onset of puberty.

The various problems and their frequency are listed below

Figure No.25: Endocrine sequelae among survivors



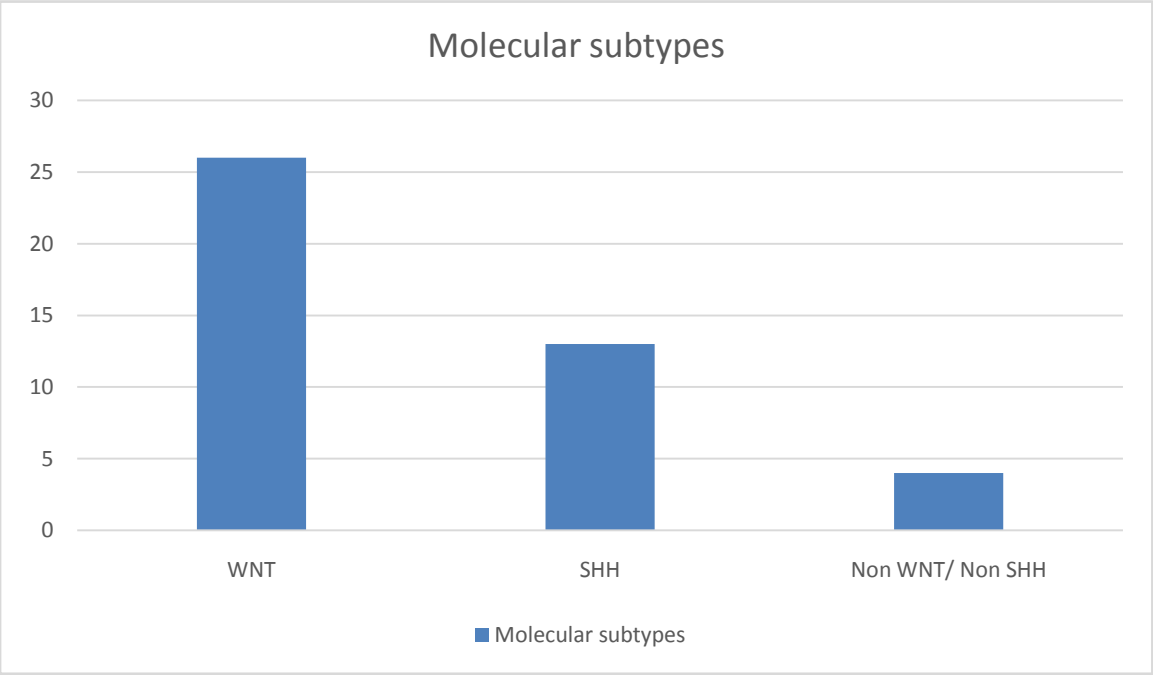
Molecular subgroups of medulloblastoma (n=43)

With immunohistochemical marker beta catenin and histology, the tumours were subdivided into various molecular subgroups in 43/76 cases. The tumours were divided into the following subgroups- WNT, SHH and non WNT/non SHH. Beta catenin was used as a immunohistochemical marker for subtyping the tumour. Nuclear beta catenin positive cases were grouped as WNT category. Tumours that were beta catenin negative and had either desmoplastic or extensive nodularity on histology constituted the sonic hedgehog (SHH) subgroup. The ones that were negative for nuclear beta catenin, and had histology other than desmoplastic/ MBEN were taken as group 3 and group 4, or non WNT/ non SHH subtype.

Table No.26: Frequency of the various molecular subtypes (n=43)

Molecular subgroup	Frequency
WNT	26
SHH	13
Non WNT/non SHH	4

Figure No. 26: Distribution of the various molecular subtypes among the patients



<u>Comparison of tumour immunohistochemistry with histology(N=43):</u>

The tumour immunohistochemistry markers were compared with histology of the tumours. 19 of the 26 WNT tumours were classic in histology, with another 2 each showing desmoplastic and large cell anaplastic histology. One patient each in WNT subgroup exhibited medulloblastoma with extensive nodularity, medullomyoblastoma and anaplastic histology. In the SHH group, 69% had desmoplastic histology, whereas 31 % was

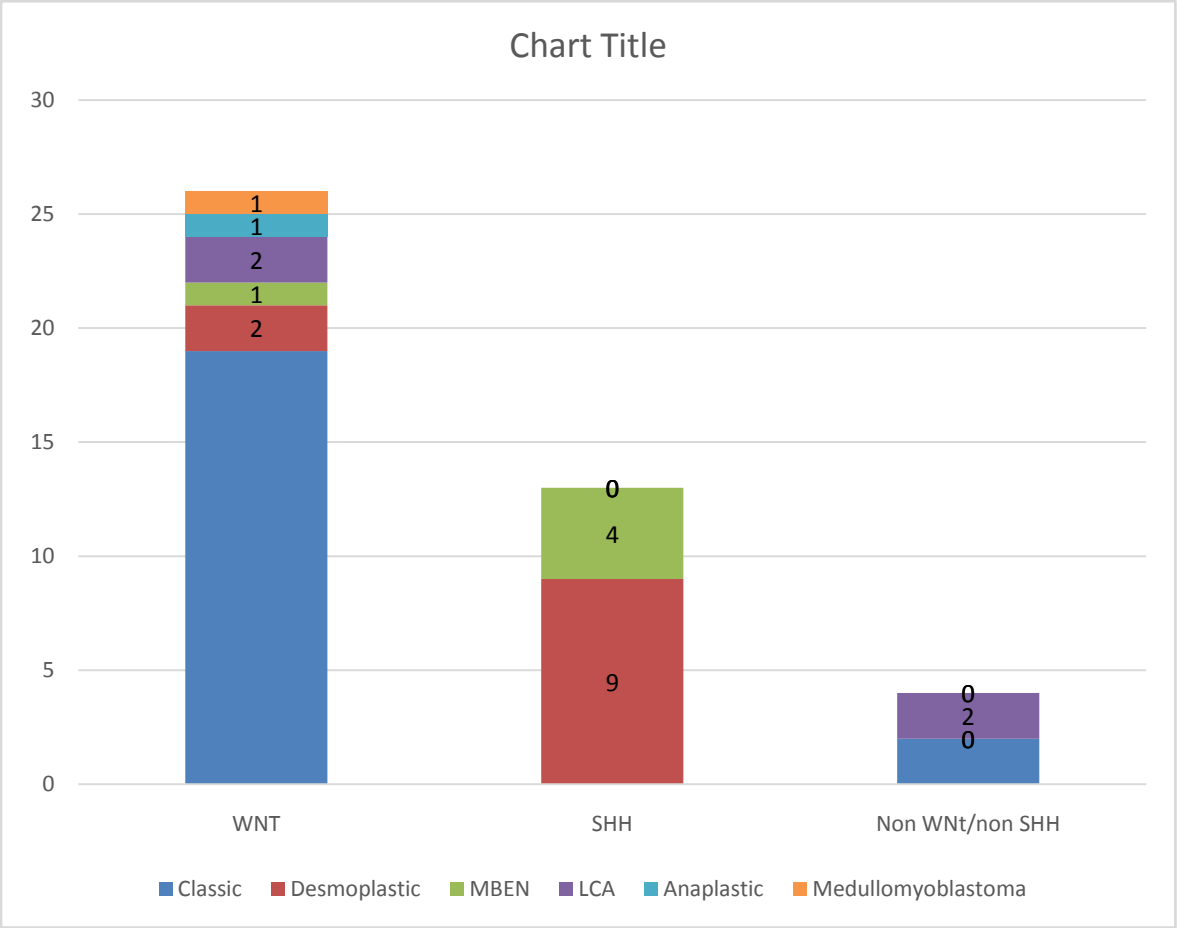
medulloblastoma with extensive nodularity. Non WNT/ non SHH group had 50 % classic histology and 50 % large cell anaplastic histology.

Table No.27: comparison of tumour IHC with histology

Tumour IHC - comparison with Histology

		HIstology						
		Classic	Desmoplastic	MBEN	Anaplastic	LCA	Medullomyoblastoma	Total
WNT		19	2	1	2	1	1	26
SHH		0	9	4	0	0	0	13
Non WNT/ Non SHH		2	0	0	2	0	0	4
		50	0	0	50	0	0	100

Figure No. 27: Different histological types within each subtype:



<u>Molecular subgroups versus risk stratification:</u>

Molecular subgroups have been known to have correlation with outcome and to be of value in prognostication of disease. On comparing molecular subgroups with the standard risk stratication as proposed by Packer et al, the following data was obtained.

Table No. 28: Molecular subgroups versus risk stratification:

Molecular subgroup	WNT(n=26)	SHH(n=13)	Non WNT/non SHHH(n=4)
Standard risk disease	15(58%)	6(46%)	1(25%)
High risk disease	11(42%)	7(54%)	3(75%)

58% of WNT subgroup belonged to standard risk group, whereas only 46% and 25 % each of SHH and non WNT/non SHH group belonged to the standard risk group. On analysing the correlation between risk stratification and molecular subgroups, it was found that there was there was result tended towards significance(p value =0.056)

Molecular subgroups versus outcome:

Tumour immunohistochemistry was used to compare the outcome between WNT, SHH and non WNT/non SHH. However, since the numbers in the third group was very small for comparison, the WNT subgroup was also compared with the non WNT subgroup which comprised of SHH subgroup as well as group 3 and group 4. Of the 43 cases with available immunohistochemistry, 26 belonged to WNT subgroup, 13 belonged to SHH and 4 to non SHH/ non WNT group. Among the 26 children in the WNT subgroup, 5 were lost to follow-up. In the SHH 5 had been lost to follow up. For the purpose of analysis, we compared WNT

group with non-WNT and it was found that WNT group had significantly better outcome.(p= 0.016).

Table No. 29: Outcome measures among the three subgroups:

Subgroup	Disease remission	Death	Recurrence	Treatment abandoned
WNT (26)	18	3	0	5
SHH (13)	3	4	1	5
Non WNT/ non SHH (4)	2	2	0	0

Since the numbers in SHH and non WNt/non SHH were very small for meaningful comparison, we combined the SHH and non WNT/non SHH group into one group, the non WNT subgroup. Further comparisons were carried out between the WNT subgroup and the non WNT subgroup.

Table No.30: Outcome measures among the WNT group and the non WNT group:

Subgroup	Disease remission	Recurrence	Death	Treatment abandoned
WNT(n=26)	18(69%)	0	3(12%)	5(19%)
Non WNT(n=17)	5(29%)	1(6%)	6(35%)	5(29%)

The above data shows that 69% of the WNT subgroup had achieved disease remission, whereas only 29% had achieved disease remission in the non WNT group. Only 12 % of

those in the WNT subgroup had died, whereas 35 % of those in the non WNT group had expired. It is quite clear from the above that the WNT group had better outcomes when compared with the non WNT group. When analyzed with anova multivariate analysis, the p value for this correlation analysis was 0.016, which means that this difference is statistically significant.

Tumour location with respect to molecular subtypes

The location of tumours and the correlation with immunohistochemistry was analysed as previous studies by Perrault et al had shown correlation between these. According to the study by Perreault, 75 % of the WNT tumours occurred along the cerebellopontine angle. SHH tumours were usually cerebellar, and group 3 and group 4 were predominantly midline, arising from the fourth ventricle. We analysed our data to see whether similar trends were present in our data as well. Tumours were classified by location into midline tumours, cerebellopontine tumours and cerebellar tumours. Of the 43 tumours which had immunohistochemistry available, 35 (81%) were midline in location, with cerebellopontine tumours and cerebellar tumours accounting for 3 (7%) and 5 (12%) each. When we compared location of tumour with various molecular subtypes, we did not find any significant correlation,(p=0.83) as 81 % of the tumours in our group were located in the midline. On analysing the location of the tumours with respect to the molecular subgroups, no correlation could be found. The p value for this analysis was 0.83.

Table No.31: Comparison of tumour location with molecular subtypes

Tumour Location	WNT	SHH	Non WNT/non SHH
Midline	22	10	3
Cerebellopontine	1	1	1
Cerebellar	3	2	0

QUALITY OF LIFE OF SURVIVORS

Quality of life of 33 of the children who are under follow up we assessed- 31 in remission, 2 on palliative treatment for recurrence. The assessment was carried out using PedsQL, a validated tool for assessment of quality of life of brain tumour survivors. The questionnaire assesses the quality of life in the following domains-physical, emotional, social and school functioning. Of these, the average of emotional, social and school functioning results is taken as the psychosocial QOL score. The total scores are the average of all domains taken into consideration. The median scores in the various domains and the total scores are listed below(all scores are on 100, with scaling from 0-100, with 0 being the worst and 100 being the maximum score indicating the best function). The module has different ones for different age groups and parent answered questionnaires as well as self answered modules. These were administered according to age and on whether child answered or the parents answered for them.

Table No.32: QOL scores among survivors who had completed treatment for medulloblastoma

Dimension	Minimum	Maximum	Mean	Standard deviation
QOL-physical	6.25	96.80	67.23	17.79
QOL-emotional	40.00	90.00	67.00	12.95
QOL-social	50.00	100.00	71.61	12.47
QOL-school functioning	20.00	95.00	62.58	15.43
QOL-psychosocial	36.66	90.00	67.25	11.51
QOL-total	33.69	92.39	67.37	12.83

Comparison of quality of life of disease-free survivors with that of those with disease recurrence:

While comparing QOL of those in CR with that of those with recurrence, there was an obvious difference with those in CR having a better QOL.

Table No.33: - Comparison of QOL scores of those with recurrence with those with disease remission:

Domain	QOL-physical	QOL-emotional	QOL-social	QOL-school	QOL-psychosocial	QOL-total
Disease remission(n=31)	69.97+/-16.11	70.17+/-11.26	73.39+/-11.55	66.25+/-10.76	69.81+/-8.52	70.01+/-10.10

Recurrence(n=2)	48.43+/-6.62	50.00+/-7.67	57.50+/-10.60	32.50+/-3.53	46.60+/-7.07	47.28+/-6.91
P value	0.04	0.043	0.076	0.018	0.02	0.03

Though the p values seem significant, since the numbers in the recurrence group is very small when compared with those in the disease remission arm, this data might not be valid.

Comparison of QOL of survivors who had tumours with WNT expression with those whose tumours did not have WNT expression:

Since there was a statistically significant survivor advantage for those in the WNT subgroup when compared with the non WNT subgroups in published literature, we compared QOL in WNT with the non WNT group. Of the 33 who had quality of life analysis, only 18 had been subdivided into WNT/ non WNT subgroups based on immunohistochemistry and histology. Analysis of the same did not reveal any significant difference.

Table No. 34: Comparison of QOL of survivors with WNT expression against those with no WNT expression

Domain	**QOL-physical**	**QOL-emotional**	**QOL-social**	**QOL-school**	**QOL-psychosocial**	**QOL-total**
WNT(n=14)	68.29+/-17.4	67.50+/-13.8	73.21+/-13.6	63.21+/-17.6	67.96+/-13.1	68.21+/-14.3
Non	74.21+/-	75.00+/-	67.50+/-	71.25+/-	70.41 +/-	72.28+/-

WNT(n=4)	9.3	9.1	6.4	11.1	6.4	6.9
P value	0.522	0.332	0.415	0.307	0.789	0.523

This might be a reflection on the fact that all children, irrespective of whether high risk or standard risk, get standard treatment according to current protocols with no escalation of treatment for high risk patients. Hence, it might be better to step down therapy for those with better prognosis to decrease the long term sequelae and to improve their quality of life.

Comparison of QOL of life of survivors who had posterior fossa syndrome in the post-operative period, with those who did not have posterior fossa syndrome in the post-operative period

Since it is well known that posterior fossa syndrome(PFS) often has prolonged effects on cognition, speech, balance, etc, QOL of survivors who had had posterior fossa syndrome were compared with that without posterior fossa syndrome. 3/11 with posterior fossa syndrome, were compared with 30 without PFS Children with PFS scored less in all domains but the numbers were too small to show a statistically significant difference between the groups.

Table No. 35: Comparison of QOL scores of those who had posterior fossa syndrome vs those who did not have posterior fossa syndrome

Domain	**QOL-physical**	**QOL-emotional**	**QOL-social**	**QOL-school**	**QOL-psychosocial**	**QOL-total**
PFS(n=3)	62.49+/-17.8	65.00+/-12.9	63.33+/-12.8	60.00+/-16.2	62.77+/-11.9	62.67+/-13.1

No PFS(n=30)	67.74+/- 20.4	68.21+/- 15.0	72.50+/- 2.9	62.85+/- 5.0	67.73+/- 6.3	67.87+/- 10.9
P value	0.545	0.611	0.111	0.377	0.284	0.348

Comparison of quality of life among those with gross total resection of tumour with those with subtotal resection of the tumour:

The quality of life of those who had gross total tumour resection was compared with those who had had subtotal tumour resection. Among the 33 patients who had quality of life assessment done, 15(45%) had undergone subtotal resection, whereas 18(55%) had undergone gross total resection. The quality of life characteristics of the group is depicted in **Table No.36: Comparison of QOL scores among those who had subtotal resection and those with gross total resection**.

Domain	**Physical QOL**	**Emotional QOL**	**Social QOL**	**School functioning QOL**	**Psychosocial QOL**	**Total QOL**
Subtotal resection(n=15)	**64.7**	**62.8**	**70.4**	**60.4**	**64.5**	**64.6**
Gross total resection(n=18)	**69.3**	**72.1**	**72.7**	**64.4**	**69.5**	**69.7**
P value	**0.486**	**0.062**	**0.619**	**0.510**	**0.277**	**0.311**

Levene's test for equality of variances was applied to the above data, to look for any significant difference between the QOL scores among the two groups. There was no statistically significant difference obtained on the analysis..

DISCUSSION

In this study we looked at clinical profile, treatment and outcome of children diagnosed to have medulloblastoma in our centre from 2004 till 2014. We also looked at the tumour immunohistochemistry of selected cases and grouped them into molecular subgroups. We then looked at the clinical profile and outcome of the various molecular subgroups as well. Assessment of quality of life of survivors was another arm of this study. There were 149 cases of medulloblastoma; 109 were in children less than 16 years of age. Only 68% (76/109) reported to the Paediatric Haematology -Oncology unit.

Clinical profile

The mean age at presentation of children in our study was 8.49 with a median age of 8 years. There were 7 children who were <3years at diagnosis. The male: female ratio was 1.8:1. This profile is similar to the series published by Packer et al (1) Most children presented with features of raised intracranial pressure. Cerebellar symptoms were less common, probably because 84% of tumours were in the midline. The mean duration of symptoms prior to presentation was 2.7 months, with a range from 1 week to 12 months. This again was similar to data from Packer et al where the mean duration of symptoms was 3 months.(1)

30% of our study population needed emergency CSF diversion procedures. Gopalakrishnan et al also found that about one third of their patients needed CSF diversion surgeries. (49)
All children underwent surgical excision of the tumour. Based on resectability and residual tumour, children were divided into those who had gross total resection vs subtotal

resection, where the residual tumour volume was >1.5cm2 vs <1.5cm2. In our group 48% (37/76) underwent gross total resection. In a series published by Gajjar et al, 50% of children with midline tumours had gross total resection.(86) Post operative complications in our study group showed meningitis in 24%, posterior fossa syndrome in 14% and CSF leak in 12%. Compared to published literature, Wells et al and Muzumdar et al had shown posterior fossa syndrome in upto 25 % of the patients after surgical resection of tumours. (23)(47)

Risk stratification

The various histological types of medulloblastoma as per WHO 2007 classification are classical, desmoplastic, medulloblastoma with extensive nodularity, anaplastic variant and large cell variant. (14). All five histological types were seen in our series too, with classical being the commonest followed by desmoplastic.

For all cases of medulloblastoma, after surgical excision of tumour further investigations are performed to ascertain risk groups. These include volume of residual tumour and localised versus metastatic disease. Residual tumour volume should be assessed using MRI scan done within 72 hours of surgery as per guidelines, but in our centre, due to various reasons, contrast CT scan is performed and there is no recommendation for ideal time for the scan as contrast enhancement will be able to differentiate between blood and residual tumour. The interval between surgery and post-operative imaging varied widely in the study group, from 1 day to 32 days after surgery, with a mean duration of 7.05 days +/-5.53. Post-operative imaging was done in 14/76(18%) before 72 hours and in the remaining 62/76(82%) it was done after 72 hours. 28/76 had no residual tumour, 18 had <1.5cm^2, 9 had 1.5-3cm^2 and in 21 the residual tumour measured more than 3cm^2. So as per risk stratification criteria based on residual disease 30/76(40%) had high risk disease.

For evaluation for metastatic disease MRI spine and CSF cytology were done. Both tests are recommended as one or the other alone reduces the pickup of metastatic disease as reported by Fouladi et al (40). 58/76 (76%) had MRI spine and 46/76 (61%) had CSF cytology and 39/76(51%) had both CSF and MRI spine done. All children had one or the other test done. 23/58 had drop metastases and 9/46 were positive for malignant cells in CSF. Based on cytology and/or MRI spine screening 27/76 (36%) had metastatic disease in this series.

Lafay Cousin et al reported the rate of metastatic disease to be 28-55% in children <3 years, compared to 15-40 % among older children(36). In our study, however, we had 28 % disseminated disease among those younger than 3 years, and 36% disseminated disease in those older than 3 years at the time of diagnosis. There was no statistically significant difference between the two groups, (p value =0.24) probably because of the smaller numbers in <3 years age group.

Metastatic disease did seem to be more frequent in those who had had a longer duration of disease(44%) , compared to those who had had symptoms for less than 3 months' duration (32%), however this did not show statistical significance (p= 0.112)

When we compared various histological types of medulloblastoma with age, residual tumour and dissemination, we did not find any significant correlation.

Overall, based on various risk stratification parameters, 10% were <3 years of age at diagnosis, 40% had residual tumour >1.5cm^2 and 36% had metastatic disease. 57% (43/76) of our patients had high risk disease.

Treatment and Outcome

The various treatment modalities for medulloblastoma include surgical excision, radiotherapy and chemotherapy. All our patients underwent surgical excision and 60 received chemotherapy and RT (if age appropriate). 21/76(28%) abandoned treatment.

Radiotherapy was well tolerated. However, chemotherapy was found to be quite toxic. Only 36/60 received 8 cycles of PCV chemotherapy. Significant side effects such as ototoxicity, cytopenia, neurotoxicity and nephrotoxicity were responsible for treatment modifications. Similar toxicity profile is reported in literature. (58-63)

50% of our patients completed treatment and 25% died of disease or other complications. 34 children were alive and were on follow up. Of these 2 were on treatment for relapse. 32/76 (42%) were in CR at the time of analysis. Data of 19 children who died showed that 14/19 (74%) had high risk disease. The mortality rate among those with standard risk disease was 15% (5/33) and those with high risk disease it was 33 %(14/43).

Outcome was compared with various risk factors; Sarkar etal , Caputy et al, verma et al described that classic histology, desmoplastic and MBEN had a better outcome compared to anaplastic type. (87, 19, 5) We also found a similar trend (p= 0.054) towards significance.

Other risk factors on outcome were not significant.

Molecular subgroups

Boston Consensus 2010 classified medulloblastoma based on their immunohistochemical properties into 4 subgroups: WNT(wingless), SHH(sonic hedgehog), Group 3 and Group 4. Each of these subtypes have distinct demographics, clinical presentation, associated genetic abnormalities as well as final outcome, as detailed by Taylor et al in their landmark paper in

Acta Neuropathologica.(6) With the help of immunohistochemical markers, the tumour can be divided into these 4 subgroups, which will not only help in prognostication, but also in targeted therapies, such as SHH inhibitors for sonic hedgehog group. (23)

We did molecular subgrouping of 43 patients using beta catenin and histology. 26/43 (60%) belonged to the WNT subgroup, 30% in SHH subgroup and 10% in non WNT/non SHH group. Our observation is quite contrary to that published by Ellison et al where only 10% was WNT, 30% SHH and 60% belong to group 3 /4 ie non WNT /non SHH. (24) It is difficult to comment on this difference as there is no published literature from India.

Comparison of molecular types with histology showed that while WNT subtype mainly consisted of classic subtype, with large cell anaplastic variant forming a small part as well, SHH was formed of desmoplastic and MBEN variants, and non SHH/ non WNT were composed of classic as well as LCA histology. This is in accordance with the accepted characteristics of these subgroups as shown by Ellison et al. (26)

On comparing the molecular subgroups with the risk stratification, assuming WNT to have good prognosis and non WNT subgroup to have poor prognosis, the analyses was shown to approach significance (p=0.056)

For analysis of outcome we compared WNT with non-WNT and found a significant difference in outcome (table no 30) p=0.016 The better prognosis associated with the WNT subgroup is very well known, as shown by Ellison et al. (32)

We compared molecular subtype with location of tumour as per radiological image. Perreault et al had shown that group 3 and group 4 tumours are mostly midline, whereas WNT tumours are usually cerebellopontine in location and SHH tumours are mostly lateral (cerebellar) in location. (38) However, in our study, 81% of all tumours were midline in location, with the remaining 19% being cerebellar and cerebellopontine. There was no correlation between the tumour location and molecular subgroups in our study.

Late effects

The delayed complications of therapy were analysed in 48 children. Cisplatin induced hearing impairment was the most common delayed complication in our group. Endocrine related complications included hypothyroidism in 19, growth hormone deficiency in 4, hypocortisolism and premature ovarian failure in two. Cisplatin induced tubulopathy presenting as hypomagnesemia and hyponatremia were rare, but interesting late effects in our group. Permanent hair loss, which was seen in 22 patients, was reported by many patients as well as parents, especially when the patients were in the adolescent age group, to be a source of embarrassment and self- consciousness in the children. 14 of these patients had sought treatment for the same, however there was no improvement noticed with the same. These late effects were also seen in other published series also (54-57, 58-62, 64-66)

Quality of life of survivors

Assessment of quality of life of survivors was done using Peds QL, a validated quality of life assessment tool, as described in the methodology. According to the mapi-organisation, a perfectly normal child would have a QOL score of 100.

The mean quality of life scores in all domains were less than 75 for all survivors, indicating that quality of life in all domains are definitely affected to some extent in all survivors. Kulkarni et al had studied the quality of life of 62 patients who had completed treatment for posterior fossa brain tumours, at a mean interval of 5.2 years after completion of treatment, using the same tool, PedsQL(84). In this study, the median score was 78.4(64.1-92.4). Our results are similar to that of Kulkarni et al. An interesting observation published by the same author states that QOL was similar in general population when compared with those who had had treatment for posterior fossa tumours. An explanation for this is probably because perceived quality of life by both survivors and care takers are much higher than functional ability of the child. This was observed by Maddrey et al (81)

Quality of life assessment of various risk groups and molecular subtypes did not any significant difference. Those with recurrence of tumour showed some difference, but the numbers were too small to draw any conclusion.

SUMMARY:

- 76 children with medulloblastoma, seen in pediatric hematology-oncology unit from 2004-2014 were included in this study, to compare clinical profile and outcome with molecular subgroups.

- The age at presentation ranged from 1 year to 15 years, with a mean of 8.49. The male: female ratio was 1.8:1. The mean age at presentation was 8.49 years. Headache, vomiting and ataxia were the common presenting symptoms. 78% of these children presented to hospital within 3 months of onset of symptoms.

- Various treatment modalities of medulloblastoma include emergency shunt surgery, followed by excision of tumour, radiotherapy and chemotherapy. All children underwent surgical excision; 29% required emergency CSF diversion surgery. 60 children received chemo-radiotherapy.

- Children with medulloblastoma were risk stratified based on age less than or more than 3 years at diagnosis, residual tumour volume of 1.5cm^2 or more and localized versuss metastatic disease. 7/76 children were less than 3 years of age at diagnosis, 30/76 had a residual tumour volume of >1.5cm^2 and 27/76 had metastatic disease. Overall, 43/76 (57%) had high risk disease.

- Molecular subgrouping of 43 children with medulloblastoma was done using beta catenin and histology. 26/43 (60%) belonged to the WNT subgroup, 30% in SHH subgroup and 10% in non WNT/non SHH group. These results were different from other published data, where WNT group was the least common.
- 60/76 received all three modalities of treatment. Rate of abandonment of treatment in this group was 21%. 34 children completed treatment and were assessed during the study. 19 children died, all except one due to disease.

- 18/33 (55%) children with standard risk disease were alive and in CR compared to 16/43(38%) with high risk disease. Mortality was found to be higher in those with high risk disease, anaplastic histology and non-WNT type of medulloblastoma, but these observations were not statistically significant.

- Late effects of treatment assessment showed high incidence of hearing impairment, hypothyroidism, alopecia and tubulopathy. Many children reported poor scholastic performance.

- Quality of life assessment done usingPeds QL, a validated quality of life assessment tool, in 33 children, where physical, emotional, scholastic, social and psycho-social domains were tested. It is proposed that a normal child will have a score close to 100. The mean total QOL score in this population was 67.4. QOL scoring was compared between various parameters such as extentof surgery, posterior fossa syndrome and those with recurrence of tumour. There was significant difference in QOL scores between those in CR compared to those with disease recurrence.

LIMITATIONS

1. Since most of the data was collected retrospectively from medical records, some relevant data was missing.

2. For molecular subgrouping of medulloblastoma, we planned to use 2 immunohistochemical markers, however only beta-catenin was standardized for use during the study period. Use of both immunohistochemistry markers would have provided more accurate subgrouping.

3. Perceived quality of life by the survivors and their parents seemed to be higher than their actual quality of life. This might represent a bias in perception on the part of the patients and their families .

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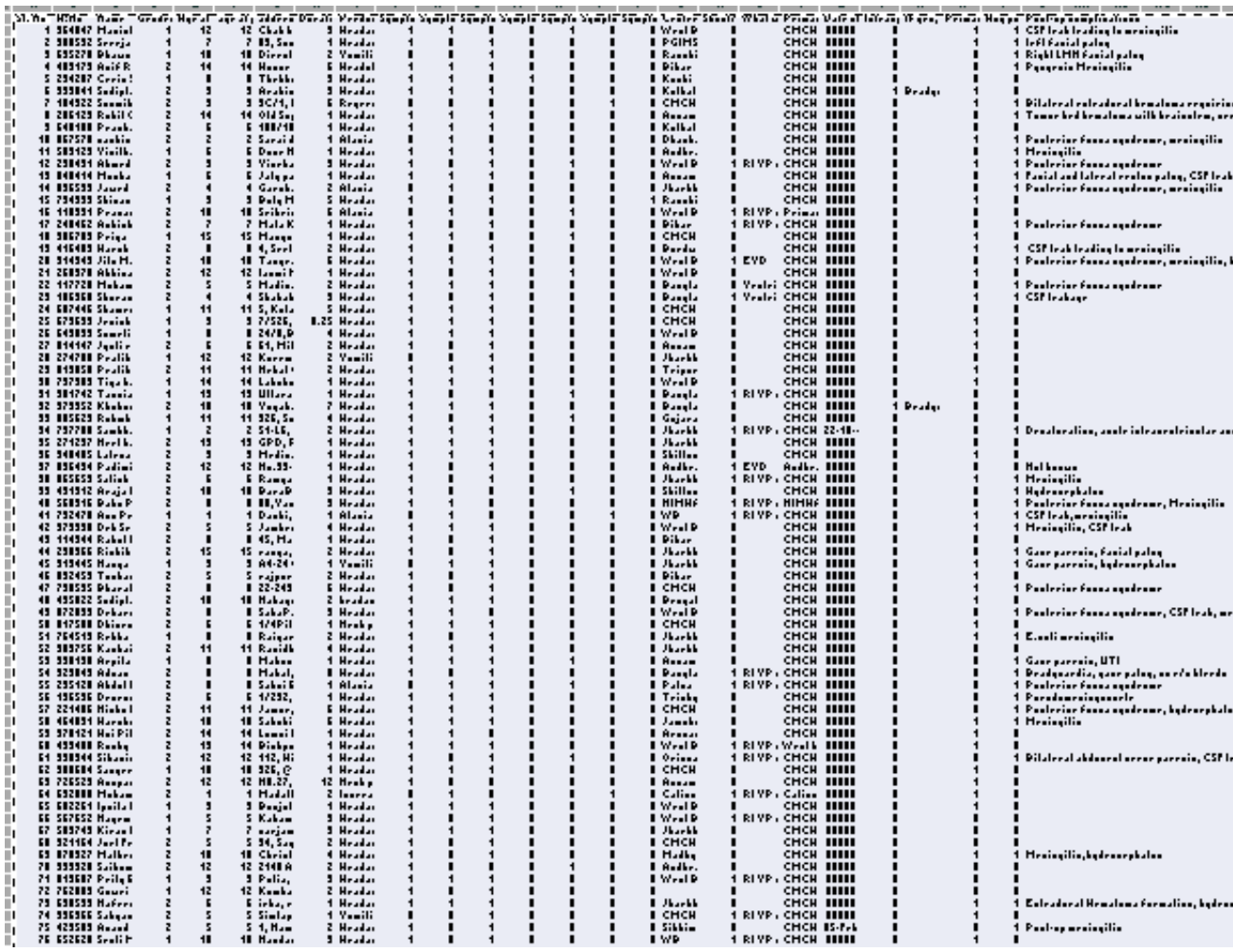
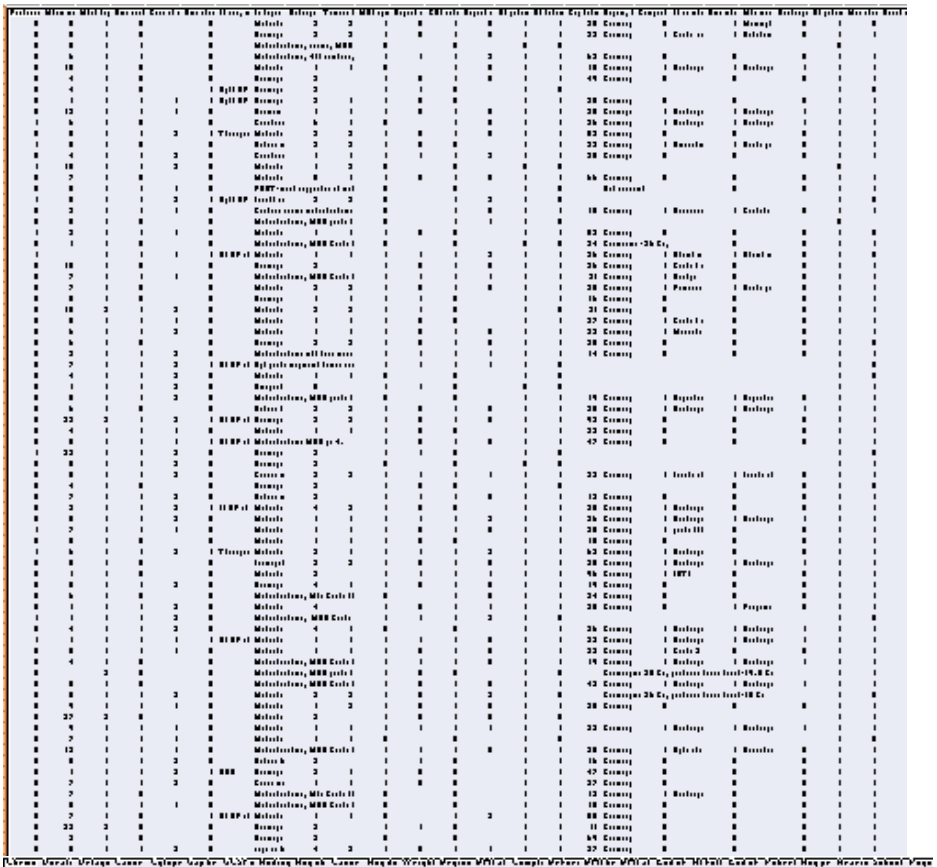
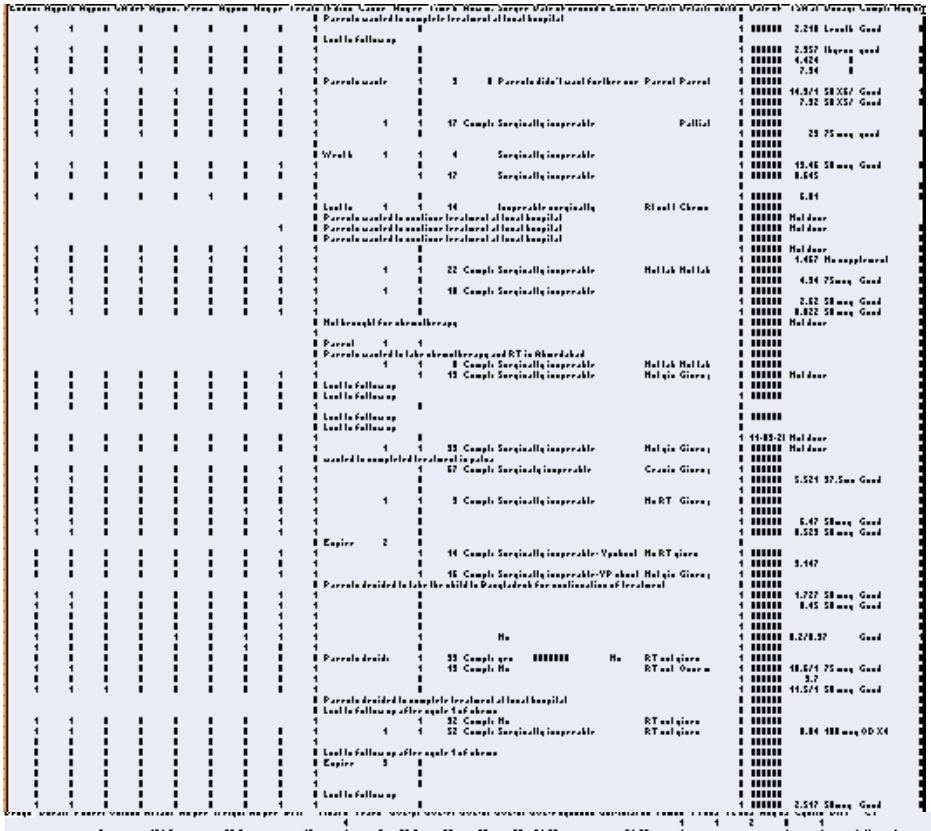
Annexures:

1. Annexure number 1: Datasheet







2. Annexure number 2: Patient information sheet:

PATIENT INFORMATION SHEET

This information sheet will explain to you the details regarding the present study. Kindly go through this carefully. You are free to clear your doubts before consenting to participate in this study.

TITLE OF RESEARCH:

Pediatric Medulloblastoma: comparing clinical profile and outcome with molecular sub groups

PERSON CARRYING OUT RESEARCH: Dr. Leenu Lizbeth Joseph

I'm Dr. Leenu Joseph, a PG registrar working in the department of paediatrics , CMC Vellore. I am doing a study on quality of life in children with medulloblastoma who were treated in the PaediatricHemato-oncology OPD between 2004 and 2014. Details of the study are given below.I would like you to be part of this study, but the choice is yours; you can decide not to take part in this study . I am happy to clarify your doubts, if there are any.

This study will be done among children who have been treated for medulloblastoma in this unit. You will be asked to fill a questionnaire regarding how you/ your child is able to carry out activities of daily living as mentioned in the questionnaire. You can clarify all your doubts regarding the questionnaire with me.

Medulloblastoma is a type of brain tumor. As you are aware your child/you was/ were treated for this in the past. We will be using information from their clinical records such as details of presenting symptoms, investigations, treatment and complications. We would like to know how you/ your child is coping with daily activities of living. For this, we would like you to answer a few questions. There

are 23 questions in this questionnaire. If you cannot understand what the question means, I can clarify your doubts for you. There are no right or wrong answers. If you feel unable to answer a certain question even after clarification, it is acceptable not to answer the same. Treatment for your child will not be altered in any way based on your answers.

CONFIDENTIALITY:

Your child's name will not be mentioned anywhere neither in the data sheet nor in the final published study. Your data will bear a study number and the number will be used till analysis. The master sheet will have your study

number.

SHARING OF THE RESULT:

The results of research are property of Christian medical college and I'm entitled to publish it in a journal or present in a conference.

This proposal has been reviewed and approved by [IRB, Christian Medical College], which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find more about the IRB,

Contact

Research Office,

Second floor, Carman block,

Christian Medical College,

Bagayam, Vellore 632002.

Email: research@cmcvellore.ac.in, Telephone: 04162284294.

It has also been reviewed by the Ethics Review Committee CMC Vellore, which is supporting the study. In case of doubts or questions, please contact Dr.Leenu Lizbeth Joseph.Department of Paediatrics, Christian Medical College and Hospital, Vellore. Ph.No.9486909752

3. Annexure number 3**: Certificate of Consent/ Assent**

I have read the foregoing information/ it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate Thumb impression (R / L)

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ and **Thumb print of participant**

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. Filling a questionnaire regarding the current functional status of my child accurately to the best of my ability
2. Participation is voluntary and there will be no extra costs/ any changes to my child's treatment/ any benefits to my child

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent-Dr. Leenu Lizbeth Joseph

Signature of Researcher /person taking the consent_____

Date _____

Annexure number 4: Permission from mapi organisation for using PedsQL

User agreement

Special Terms

Mapi Research Trust, a non-for-profit organisation subject to the terms of the French law of 1st July 1901, registered in Carpentras under number 453 979 346, whose business address is 27 rue de la Villette, 69003 Lyon, France, hereafter referred to as "Mapi" and the User, as defined herein, (each referred to singularly as a "Party" and/or collectively as the "Parties"), do hereby agree to the following User Agreement Special and General Terms:

Mapi Research Trust
Information Support Unit
27 rue de la Villette
69003 Lyon
France
Telephone: +33 (0)4 72 13 65 75
Fax: +33 (0)4 72 13 66 82
Email: PROinformation@mapi-trust.org

Recitals

The User acknowledges that it is subject to these Special Terms and to the General Terms of the Agreement, which are included in Appendix 1 to these Special Terms and fully incorporated herein by reference. Under the Agreement, the Questionnaire referenced herein is licensed, not sold, to the User by Mapi for use only in accordance with the terms and conditions defined herein. Mapi reserves all rights not expressly granted to the User.

The Parties, in these Special Terms, intend to detail the special conditions of their partnership.

The Parties intend that all capitalized terms in the Special Terms have the same definitions as those given in article 1 of the General Terms included in Appendix 1.

In this respect, the Parties have agreed as follows:

Article 1. Conditions Specific to the User

Section 1.01 Identification of the User

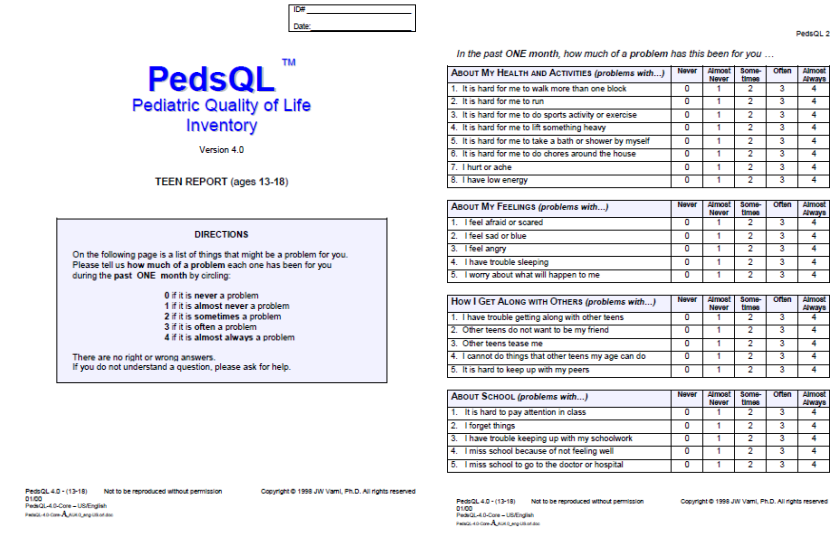
User name	**Leenu joseph**
Legal Form	Leenu Joseph
Address	department of child health, Christian medical college, vellore
Country	India

Name of the contact in charge of the Agreement	**Leenu Joseph**
Telephone number	0416-2283350
Fax number	
Email address	leenujoseph@gmail.com
If different:	
Legal Form	
Address	
Country	

Section 1.02 Identification of the Questionnaire

Title	Pediatric Quality of Life Inventory™ (PedsQL™)
Author(s)	Varni James W, PhD
Owner	Varni James W, PhD

1. Annexure number 5: PedsQL



ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

TEEN REPORT (ages 13-18)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

In the past ONE month, how much of a problem has this been for you …

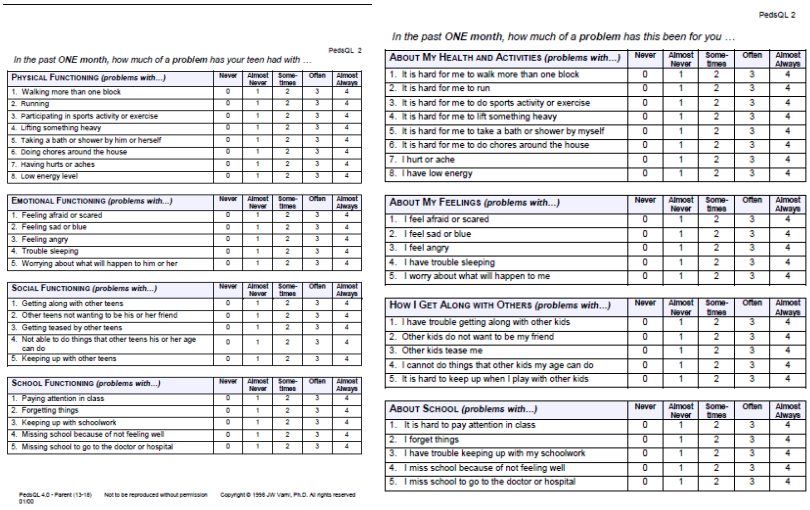
About My Health and Activities *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About My Feelings *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I Get Along with Others *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

About School *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

PedsQL 4.0 - (13-18) Not to be reproduced without permission Copyright © 1998 JW Varni, Ph.D. All rights reserved
01/00
PedsQL-4.0-Core – US/English



PedsQL 2

In the past ONE month, how much of a problem has your teen had with …

Physical Functioning *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

Emotional Functioning *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

Social Functioning *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that other teens his or her age can do	0	1	2	3	4
5. Keeping up with other teens	0	1	2	3	4

School Functioning *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

PedsQL 2

In the past ONE month, how much of a problem has this been for you …

About My Health and Activities *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About My Feelings *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I Get Along with Others *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

About School *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4